NEUROPSYCHOLOGICAL CORRELATES OF CHRONIC FATIGUE SYNDROME

by

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ABSTRACT

Neuropsychological deficits have been implicated in Chronic Fatigue Syndrome (CFS) and there is some indication that cerebral efficiency is compromised in these patients. To further investigate the nature of this impairment, 20 patients who had received a medical diagnosis of CFS were neuropsychologically assessed and compared with age-, sex-, and education-matched controls (20 depressed and 20 healthy subjects). The test battery consisted of the Grooved Pegboard, Trail Making Test, Symbol Digit Modalities Test, Auditory-Verbal Learning Test, Visual Design Learning Test, Controlled Oral Word Association Test and Paced Auditory Serial Addition Task. Additional measures included a CFS symptom checklist, SCL-90-R and Cognitive Failures Questionnaire (CFQ). Univariate statistical analysis revealed a significant difference between CFS patients and healthy individuals on only one measure; the "S" trial of the COWAT (F [2,59] = 3.30, p <.05). This finding suggests the existence of subtle but detectable neuropsychological difficulty in executive or attentional mechanisms in CFS patients. Further analysis revealed that the observed finding could not be attributed to depression or medication side-effects. Although a trend of declining neuropsychological test performance was evident in moving across the spectrum of healthy, depressed, and CFS samples, this reached significance only for the CFS/depressed versus healthy comparison (χ_2^2 [1] = 9.40, p < .05). The overall similarity of the neuropsychological profiles of CFS and depressed patients was noted, while an additional finding was the discrepancy between reported levels of subjective cognitive failure (CFQ) and objective neuropsychological findings in the CFS patients.

The SCL-90-R profiles of the CFS and depressed patients were also found to be similar in terms of reported levels of psychological distress; however group discrimination was evident on two subscales (*Somatization* and *Obsessive-Compulsive*). Although the CFS and depressed controls did not differ with respect to levels of depression, there were some indications of a differential impact of depressive symptomatology on neuropsychological functioning.

Taken together, the results of this study indicate that while subtle deficits are detectable in the neuropsychological profiles of CFS patients, the magnitude of impairment appears insufficient to significantly interfere with everyday cognitive functioning.

PREFACE

The experimental work described in this thesis was carried out in the Department of Psychology, University of Natal, Pietermaritzburg, from May 1991 to August 1997, under the supervision of Dr. Michael Budek and Professor Graham Lindegger.

This study represents original work by the author and has not otherwise been submitted in any form for any degree or diploma to any University. Where use has been made of the work of others, it is duly acknowledged in the text.

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LIST OF CONTENTS

Introduction, 1

CHAPTER 1: CHRONIC FATIGUE SYNDROME: CONCEPTUAL ISSUES, 4

1.1 *Historical Perspective*, 6

1.1.1 Early History, 6

1.1.2 The "Second Wave", 11

1.1.3 Recent History (1978-1988), 16

1.1.4 Case Definitions (1988-1991), 19

1.2 *Clinical Presentation of CFS*, 27

1.2.1 Diagnostic Difficulties, 27

1.2.2 Symptoms and Signs, 31

1.2.3 Laboratory Findings in CFS, 36

1.2.4 Epidemiology, 39

1.2.5 Pediatric and Adolescent CFS, 44

1.2.6 Course and Outcome, 46

1.2.7 Differential Diagnosis, 49

1.3 *The Pathogenesis of Chronic Fatigue Syndrome*, 58

1.3.1 Viral Infection, 58

1.3.2 Is CFS an Interactive Infection? 63

1.4 *Treatment Issues*, 65

1.4.1 Pharmacological Therapies, 65

1.4.2 Non-Pharmacological Therapies, 68

1.4.2.1 Psychological Interventions, 68

1.4.2.2 Activity Management, 69

1.4.2.3 Alternative Treatments, 70

1.4.3 Composite Approaches, 71

1.5 *The Nature of Fatigue*, 73

1.5.1 Psychological (Mental) Fatigue, 74

1.6 *Current Status of CFS*, 77

CHAPTER 2: CHRONIC FATIGUE SYNDROME, PSYCHOPATHOLOGY AND PSYCHONEUROIMMUNOLOGY, 80

2.1 *Chronic Fatigue Syndrome and Psychiatric Illness*, 81

2.1.1 CFS and Depression, 91

2.2 *Abnormal Illness Behaviour, CFS, and Psychoneuroimmunology*, 95

2.2.1 Psychoneuroimmunology, 99

2.2.2 Psychosocial Factors and CFS, 101

2.3 *Conclusion.* 104

CHAPTER 3: THE NEUROBIOLOGY OF CFS, 105

3.1 *CNS Effects of Viral Infection*, 106

3.2 *Specialized Investigative Techniques*, 114

3.2.1 Electrophysiology, 114

3.2.2 Neuroimaging, 116

3.3 *Other Biological Investigations*, 121

3.4 *The Pathophysiology of Fatigue (the "Muscle versus Brain" Debate)*, 122

3.5 *Immune System Functioning in CFS*, 127

3.6 *Biological Aspects of Psychoneuroimmunology*, 135

3.7 *Is there a Biological Basis to Chronic Fatigue Syndrome?* 140

CHAPTER 4: THE NEUROPSYCHOLOGY OF CHRONIC FATIGUE SYNDROME: CURRENT PERSPECTIVES, 143

4.1 *Neuropsychological Investigations*, 145

4.2 *The Neuropsychology of Depression*, 157

4.3 *Conclusions*, 159

CHAPTER 5: THE NEUROPSYCHOLOGICAL PARADIGM AND STATEMENT OF AIM, 162

5.1 *Issues in the Current Practice of Neuropsychology*, 162

5.2 *Rationale for the Current Study and Statement of Aim*, 168

CHAPTER 6: METHODOLOGY, 170

6.1 *Considerations in the design of CFS research studies*, 170

6.1.1 Research Strategy, 170

6.1.2 Patient Variables, 172

6.1.3 Assessment of Fatigue, 173

6.1.4 Selection of Neuropsychological Tests, 174

6.2 *Neuropsychological Tests Used in the Current Study,* 179

6.2.1 Trail Making Test (TMT), 179

6.2.2 Symbol Digit Modalities Test (SDMT), 180

6.2.3 Grooved Pegboard, 181

6.2.4 Paced Auditory Serial Addition Task (PASAT), 181

6.2.5 Controlled Oral Word Association Test (COWAT), 183

6.2.6 Memory Tests, 184

6.3 *Psychological Questionnaires*, 190

6.3.1 Symptom Checklist 90-R(evised) (SCL-90-R), 191

6.3.2 Cognitive Failures Questionnaire (CFQ), 193

6.3.3 CFS Symptom Checklist, 194

6.3.4 Intake Questionnaire, 195

6.4 *Study Subjects*, 196

6.4.1 CFS Subjects ($n = 20$), 197

6.4.2 Depressed Subjects ($n = 20$), 198

6.4.3 Healthy Controls ($n = 20$), 200

6.5 *Procedure*, 202

6.6 *Treatment of Raw Data*, 206

CHAPTER 7: RESULTS, 207

7.1 *Overview and Rationale of Statistical Analysis*, 207

7.2 *Reliability*, 210

7.3 *Psychological Questionnaires*, 210

7.3.1 Intake Questionnaire, 210

7.3.2 CFS Symptom Checklist, 213

7.3.3 Cognitive Failures Questionnaire (CFQ), 215

7.3.4 Symptom Checklist 90-R(evised) (SCL-90-R), 219

7.4 *Neuropsychological Findings*, 223

7.5 *Prevalence of Neuropsychological Impairment*, 231

CHAPTER 8: DISCUSSION AND CONCLUSION, 235

8.1 *Psychological Findings*. 235

8.1.1 CFS Symptomatology, 235

8.1.2 Cognitive Failures Questionnaire (CFQ), 236

8.1.3 Symptom Checklist 90-R(evised) (SCL-90-R), 237

8.2 *Neuropsychological Findings*, 240

8.2.1 Group Comparisons Using ANOVA, 240

8.2.2 Neuropsychological Impairment Ratings, 245

Conclusion, 249

Limitations of the Current Study and Suggestions for Future Research, 251

REFERENCES, 254

APPENDICES, 294

Appendix A: Intake Questionnaire, 294

Appendix B: Cognitive Failures Questionnaire, 301

Appendix C: CFS Symptom Checklist, 302

Appendix D: Subject Demographic Variables, 304

Appendix E: Psychometric Summary Score Sheet, 306

Appendix F: Variables List, 307

LIST OF TABLES

Table 1-1. Clinical Characteristics Observed in 20 Patients with Severe CFS, 17

Table 1-2. Operational Criteria for CFS as Proposed by Lloyd et al. (1988), 20

Table 1-3. CDC Diagnostic Criteria for Chronic Fatigue Syndrome, 22

Table 1-4. Research Diagnostic Criteria for CFS, 25

Table 1-5. Range and Frequency of Reported Symptoms in Patients with CFS, 32

Table 1-6. Physical Findings in CFS Patients, 35

Table 1-7. Recommended Laboratory Tests and Representative Findings in CFS, 37

Table 1-8. Differential Diagnosis of Chronic Fatigue Syndrome, 50

Table 1-9. Discriminating Features of Fibromyalgia and CFS, 54

Table 1-10. Viruses Implicated in CFS, 59

Table 1-11. Revised CDC Criteria for Chronic Fatigue Syndrome, 78

Table 2-1. Studies Investigating Psychological/Psychiatric Aspects of CFS, 83

Table 3-1. Immunologic Abnormalities Reported in CFS, 131

Table 4-1. Representative Neuropsychological Investigations of CFS by Tests Used, 146

Table 4-2. Neuropsychological Correlates of Depression, 158

Table 5-1. Areas of Neuropsychological Function and Representative Tests in a Typical Test Battery, 164

Table 5-2. Classification of Ability Levels, 166

Table 6-1. A Representative Neuropsychological Test Battery for CFS, 175

Table 6-2. Word Lists and Story Recognition Format from the Auditory-Verbal Learning Test, 186

Table 6-3. Symptom dimensions of the Symptom Checklist 90 - R(evised), 192

Table 6-4. Inclusion Criteria for Depressed Control Group, 199

Table 6-5. Demographic Profiles of Subjects Used in the Current Study ($N = 60$), 201

Table 6-6. Demographic Breakdown (Age by Education) of Study Subjects ($N = 60$), 201

Table 7-1. Intake Questionnaire Data (Sample Percentages) by Group (CFS, Depressed, Healthy), 211

Table 7-2. Frequency of Reported Symptoms from the Symptom Checklist by Group (CFS, Depressed, Healthy), 214

Table 7-3. Cognitive Failures Questionnaire Scores (Mean and *SD*) by Group (CFS, Depressed, Healthy), 215

Table 7-4. CFQ Discriminant Function Analysis Classification Matrix, 217

Table 7-5. CFQ Items Showing the Highest DFA Group (CFS, Depressed, Healthy) Classification Ability, 218

Table 7-6. SCL-90-R Scores (Mean and *SD*) by Group (CFS, Depressed, Healthy), 219

Table 7-7. SCL-90-R Discriminant Function Analysis Classification Matrix, 221

Table 7-8. Mean SCL-90-R *Depression* Subscale *T*-Scores (*SD* in Parentheses), and Frequency of *T*-Scores > 70 for the CFS, Depressed and Healthy Groups, 222

Table 7-9. Neuropsychological Test Scores (Mean and *SD*) by Group (CFS, Depressed, and Healthy), 223

Table 7-10. Correlation Matrix Showing the Significant Associations Between the Neuropsychological Test Scores and SCL-90-R *Depression* subscale (Raw Score), 230

Table 7-11. Neuropsychological Ratings for CFS, Depressed and Healthy Subjects, 232

LIST OF FIGURES

Figure 1-1. Clinical Course of CFS: Acute versus Gradual Onset, 46

Figure 2-1. Hypothetic Model of CFS Perpetuation (Sharpe, 1993), 98

Figure 3-1. Proposed Model for the Pathogenesis of CFS (Keller et al., 1994), 140

Figure 7-1. Graphical Representation of CFQ Items Showing Highest DFA Group Classification Ability, 218

Figure 7-2. SCL-90-R *T*-Score Profiles for CFS and Control Groups, 220

Figure 7-3. Histogram Showing Relative Percentages of Positive Cases on the SCL-90-R, 221

Figure 7-4. COWAT Profiles for CFS and Control Groups, 226

Figure 7-5. AVLT Profiles for CFS and Control Groups, 226

Figure 7-6. PASAT Performance Over Trials; CFS versus Control Groups, 227

Figure 7-7. AVLT Performance Over Trials; CFS versus Control Groups, 228

Figure 7-8. AVLT Performance Over Trials; CFS versus Control Groups, 228

Figure 7-9. Distribution of Overall Neuropsychological Performance by Group (CFS, Depressed, Healthy), 231

Figure 7-10. Mean Neuropsychological Summary Impairment Ratings (SIR) for CFS and Control Groups, 234

INTRODUCTION

Chronic fatigue syndrome (CFS) is a controversial diagnostic entity that may include both somatic and psychological symptoms. The cardinal feature is profound fatigue of more than six months duration that causes a reduction in the capacity to perform daily activities, and which affects both physical and mental functioning (Sharpe et al., 1991). Additional symptoms include multiple muscular, systemic and neuropsychological complaints. The coexistence of psychopathology (especially depression) in some cases has created conceptual and diagnostic difficulties for the medical and psychological professions. There have been consistent attempts to identify biological markers of the illness and although a viral cause is suspected, none have emerged as unequivocal proof of a pathognomic process (Ablashi, 1994). More recent research has focussed on the nature of immunological disturbance that has come to be associated with CFS (Barker, Fujimura, Fadem, Landay, & Levy, 1994; Demitrack, 1994). Available evidence indicates that CFS involves a complex relationship between immune system functioning, physiology and psychological processes.

A variety of different research paradigms have been employed to gain insight into CFS. For example, recent biological investigations have used magnetic resonance imaging (MRI), single photon emission tomography (SPECT), electrophysiological methods, myographic and virological approaches to provide greater understanding of the possible biological bases of the syndrome. In contrast, individual and social dimensions of CFS have attracted attention from psychiatrists and psychologists as possible precipitants and mediators of symptomatology. Despite these diversified attempts, many questions remain unanswered, and it seems reasonable to predict that the controversy, and hence research into the nature and cause of CFS, will continue for some time to come.

The focus of this study is the neuropsychological dimension of CFS. A number of neuropsychological complaints have been associated with CFS, and include diminished attention, concentration problems, forgetfulness, irritability and difficulty in thinking (Holmes et al., 1988). These subjective impairments are reported by up to 90% of affected individuals and are frequently

cited as the reason for diminished occupational functioning (Komaroff & Buchwald, 1991). The neurocognitive profile of patients with CFS has been investigated in a number of recent investigations. Some studies have found generally normal neuropsychological functioning (Altay et al., 1990; Schmaling, DiClementi, Cullum, & Jones, 1994). In those studies that have found evidence of impairment, the degree of dysfunction is typically modest. Nevertheless, reduced neuropsychological competence has been reported for attentional and vigilance functions, memory and learning ability, psychomotor performance, intellectual functioning, and speed of information processing (Bastien, Peterson, & Watson, 1996; Cope, Pernet, Kendall, & David, 1995; DeLuca, Johnson, Beldowicz, & Natelson, 1995; DeLuca, Johnson, & Natelson, 1993; Grafman et al., 1993; Johnson, DeLuca, Fiedler, & Natelson, 1994; Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; Marshall, Forstot, Callies, Peterson, & Schenk, 1997; Marshall et al., 1996; McDonald, Cope, & David, 1993; Michiels, Cluydts, Fischler, Hoffman, Le Bon, & De Meirleir, 1996; Ray, Phillips, & Weir, 1993; Riccio, Thompson, Wilson, Morgan, & Lant, 1992; Sandman, Barron, Nackoul, Goldstein, & Fidler, 1993; Smith, Behan, Bell, Millar, & Bakheit, 1993).

Inter-study variability (in terms of methodology and comparison groups), makes it difficult to draw firm conclusions about the nature of the neuropsychological difficulties experienced by CFS patients; nevertheless, there is reasonable consensus that test performance is characterized by reduced cerebral efficiency and that this is primarily manifested on measures of information processing. Additionally, there is some evidence that concurrent depression and fatigue may have a moderating effect on neuropsychological functioning in at least some CFS patients (Cope et al., 1995; McDonald et al., 1994; Ray et al., 1993).

The current study was conceptualized in 1991, at a time when there were few published studies on the neuropsychological aspects of CFS and little was known about the nature and extent of subjective cognitive complaints made by patients with CFS. To date, there have been at least 19 investigations into the neuropsychological dimensions of this illness, the majority of which were published after the initiation of data collection in the current study. However, only five studies (Cope et al., 1995; DeLuca et al., 1995; Marshall et al., 1997 Sandman et al., 1993; and Schmaling et al., 1994) have attempted to contrast CFS patients with depressed controls, and

few studies have attempted to match the control groups on more than one or two variables in a case-control design. In addition, no other study has employed exactly the same combination of measures to study neuropsychological functioning.

The overall aim of the current thesis was to assess the neuropsychological functioning of patients with CFS. It was hoped that if a distinct neuropsychometric profile could be identified, this could have diagnostic and case management relevance. At the time of study conceptualization, an hypothesis of viral infection with subsequent immune dysfunction was, and still is, a popular explanation for CFS symptomatology. Given that viral infection can challenge the integrity of normal brain function, it was reasoned that an examination of neuropsychological functions might reveal evidence of a sub-clinical or chronic viral infection. Because of the often vague and transient nature of some cognitive complaints in CFS, the current study employed measures that would cover a wide range of neuropsychological functions but still be sensitive to specific and subtle impairment. Since neuropsychological deficits have been documented in depressed individuals, it was expected that impairment would be present in both CFS and the depressed control group. However, given the possible viral etiology in CFS, it was hypothesized that neuropsychological functioning would be at least qualitatively different in the two groups.

Because the focus of this thesis is on the neuropsychological dimension of CFS, the literature review is organized in such a way that emphasis is placed on certain concepts relevant to the study of this dimension. Hopefully this will not detract from the view that CFS is a complex and multifaceted illness and that under-emphasis of certain dimensions does not imply lack of importance. The first two chapters examine the clinical presentation and psychological/psychiatric dimensions of CFS, while the neurobiological and neuropsychological investigations of CFS are the topics of Chapters 3 and 4 respectively. The literature review ends with a brief synopsis of the neuropsychological paradigm and statement of aim (Chapter 5). The methodology chapter explores some of the issues around CFS research and specifies the nature of the study sample and data collection. The results are presented in Chapter 7.

CHAPTER 1

CHRONIC FATIGUE SYNDROME: CONCEPTUAL ISSUES

> "It is all too apparent that although enormous advances have been made in biomedical research, the enigma of epidemic neuromyasthenia remains quite as puzzling a problem as it was 35 years ago" (Henderson, 1994, p. 6).

Unlike many illnesses where there is a clear cut etiology, clinical presentation and treatment, CFS remains somewhat elusive to attempts to categorize it in this way. The varied symptomatology associated with the illness and the absence of distinct physical signs in many cases have led to much debate about its etiology. Various arguments have been put forward for classifying the condition as a persistent viral infection (Behan, Behan, & Bell, 1985; Dowsett, Ramsay, McCartney, & Bell, 1990), as an immune dysregulation disease (Demitrack & Greden, 1991), and as a psychiatric disorder (David, Wessely, & Pelosi, 1988; Taerk, Toner, Salit, Garfinkel, & Ozersky, 1987). Furthermore, it is generally accepted that chronic fatigue is not unique to CFS; other conditions such as cancer, diabetes, hepatitis, brucellosis, systemic lupus erythematosus, cholera influenza, total allergy syndrome, and depression can give rise to fatigue states that are largely indistinguishable from CFS (Bell 1994; Rikard-Bell & Waters, 1992). Clinicians are even divided about whether CFS is a valid clinical entity although Strauss (1991) makes the interesting observation that a number of articles which attempt to explain the non-existence of a discrete and separate disease entity such as CFS, often conclude with criteria for making the diagnosis. In order to appreciate the conceptual complexity of CFS, one does not have to look further than the titles of articles appearing in the published literature. For example, the professional and public literature is replete with titles such as:

> "The trouble with ME."
> "Royal Free Disease: perplexity continues."
> "Chronic fatigue syndrome controversy."
> "The chronic fatigue syndrome: what do we know?"

"Myalgic encephalomyelitis - is it a real disease?"

"Chronic fatigue syndrome: is it real?"

"Postviral fatigue syndrome: time for a new approach."

"The chronic fatigue syndrome: a return to common sense."

"The chronic fatigue syndrome - myth or mystery?"

"The chronic fatigue syndrome - one entity or many?"

"Chronic fatigue syndrome: a conundrum."

"M.E. - in mind or body."

The difficulty lies in the fact that the symptoms of chronic fatigue are not confined solely to either an organic or functional state, but can be conceptualised as spanning a physiological and psychological spectrum (Komaroff & Buchwald, 1991; Riccio et al., 1992). Differential diagnoses include many well-recognized medical illnesses on the one hand, and various psychological conditions on the other. Sharpe et al. (1991) suggested that this lack of clarity could only be resolved through a multifactorial approach with adherence to rigorous research methodologies. Unfortunately, it seems that CFS research since 1988, when the diagnostic criteria for CFS were first published, has been limited by heterogenous patient samples and diverse methodological approaches.

This section of the literature review examines some of the conceptual issues surrounding the label of chronic fatigue syndrome. It covers the history of the illness, symptoms and signs, etiology and diagnosis, epidemiology, treatment issues and outcome, nature of fatigue, and ends with a synopsis of the current status of CFS.

1.1 HISTORICAL PERSPECTIVE

The symptoms of CFS have been described under many different labels. These include Icelandic (Akureyri) disease, epidemic neuromyasthenia, Addington Disease, neurasthenia, benign or epidemic myalgic encephalomyelitis (ME), Royal Free Disease, chronic Epstein-Barr virus syndrome (CEBV), idiopathic chronic fatigue and myalgia syndrome, atypical polio, chronic infectious mononucleosis, "yuppie flu", chronic fatigue syndrome (CFS), post-viral fatigue syndrome (PVFS) and more recently, chronic fatigue immune dysfunction syndrome (CFIDS). Fairly consistent use of the term "chronic fatigue syndrome" is evident from the more recent British publications and is the reference term used throughout this thesis. It is noted however that the preferred descriptor in North America is CFIDS (pronounced "see-fids"), a term consistent with findings of a dysfunctional immune system in CFS patients (Tavris, 1991).

The idea that CFS is a modern-day illness associated with high-achieving, young professionals (so-called "yuppies") is not substantiated by the literature and as will be evident shortly, epidemiological studies implicate a wide range of affected persons from virtually all age groups and widely dispersed socioeconomic and geographical regions. Moreover, despite recent increases in the incidence of CFS, exhaustion and debilitating fatigue have been presenting complaints seen by the medical profession for a few hundred years (Shorter, 1993).

1.1.1 Early History

Although a 2000-year-old Chinese medical text describes symptom complexes similar to the present day conception of CFS, "vapours" was probably the first term used to describe chronic fatigue, and it apparently appeared in the medical literature in 1662 (Wilson, 1990). Nevertheless, credit for the first case study report to appear in the medical literature has been given to Sir Richard Manningham who presented a paper in 1750. He described an illness (febricula) in which the presenting symptoms included "little low, continued fever ... little transient chilliness ... listlessness with great lassitude and weariness all over the body ... little flying pains ... sometimes the patient is a little delirious and forgetful" (as cited in Straus, 1991, p. 2).

Furthermore, Manningham considered the syndrome to be most prevalent in wealthy women who were sedentary and studious, and that the illness was precipitated by various events such as grief, intense thoughts and taking cold. In 1793, the German physician Eberhard Gmelin described one of his young female patients who was too weak to get out of bed: "She is able to remain out of bed for only a very short time, sitting on a chair; nor is she able, without being supported by someone, to go from one chair to the next" (as cited in Shorter, 1993, p. 7). Hypnosis was a popular treatment for such cases, and on giving her a glass of "magnetized" water to drink, Gmelin reported that she was "able to dress herself, to run unaided and quickly to her friends in the adjoining room, and claimed that she desired to go dancing" (ibid). Unfortunately, once the hypnotic trance was over she apparently lapsed back into her weakened state

It is difficult to know how much importance to attach to these early reports. Shorter (1993) is sceptical of the validity of such cases; he emphasizes that physicians prior to 1900 experienced difficulty in distinguishing psychogenic weakness from neurogenic weakness, and were possibly less astute in differentiating chronic idiopathic fatigue from melancholia (depression) than were subsequent physicians.

The second half of the 19th century saw an increase in the number of reported cases of patients with debilitating weakness and fatigue; Shorter cites a variety of illustrative case studies first described by Wilks (1869). For example, physician Charles Taylor in 1864 mentions a number of cases of mainly upper-middle-class female patients who were bed-ridden with profound fatigability of mind and body. One such patient was Alice James, the sister of author Henry James, who was apparently too weak to arise from bed. In another case described in 1867, Dr Eduard Levinstein saw a 36 year-old woman who had been in bed for 11 years because of muscle weakness and fatigue. She was also hypersensitive to light and showed slowed thinking. Levinstein admitted her to a sanatorium where her recovery followed treatment with hot baths and encouragement. This led to the speculation by Levinstein that her symptoms were psychogenic (i.e. functional) rather than somatogenic (i.e. organic). Dr Samuel Wilks also supported a psychogenic etiology for a number of cases he saw in 1869. The typical presentation was described as in the following way:

> she has taken to her bed as if for the remainder of her days, and all is arranged accordingly - the stitching, the embroidery, the religious books where they can be comfortably reached, and she generally receives more sympathy from the clergyman and the lady visitors than do cases of real illness.
>
> (as cited in Shorter, 1993, p. 8).

While only a sample of representative cases are presented above, Thomas (1993) maintains that in the last decades of the 19th century there were substantial numbers of middle-class female patients who were bed-ridden with symptoms of chronic fatigue and muscle weakness. He refers to this apparent epidemic as the "first wave of chronic fatigue."

The term "neurasthenia" was used to describe later cases, and appeared in the medical literature between 1860 and 1880 (Wessely, 1991). The precursor of this term was "nervous exhaustion" which was apparently used to describe cases characterized by chronic fatigue (Straus, 1991). George Beard (an American neurologist) was apparently unhappy with this term and so, believing it to be inadequately scientific, changed it to neurasthenia. His book, *American Nervousness* was published in 1869 (ibid). In Beard's view, neurasthenia was a physical illness due to actual loss of nerve strength. The essential features of Beard's conceptualization of neurasthenia are described by Cobb in 1920 as a condition characterized by "undue fatigue on slightest exertion, both physical and mental, with which are associated symptoms of abnormal functioning, mainly referable to disorders of the vegetative nervous system. The chief symptoms were headache, gastrointestinal disturbances, and vague subjective sensations of all kinds (as cited in Wessely, 1991a, p. 920). This symptom cluster must have had some appeal for the Victorian physicians, since Shorter (1993) notes that by 1900, neurasthenia had become the single most common diagnosis in the fields of neuropathology and psychopathology. One possible reason for its popularity may have been the appearance of the "first wave of chronic fatigue" at a time when psychiatry was establishing itself as a discipline. In explaining the sudden appearance of this "first wave" of neurasthenia or chronic fatigue, it is possible that as the Western world became rapidly industrialized, neurasthenia represented a psychosocial reaction to resistance to change. In this context, Greenberg (1990) reports that neurasthenia became common in America as a result of the stress inherent in a competitive, capitalistic society.

Apart from the core symptoms of mental and physical fatigue, Beard was also able to comment on some demographic variables and etiology, i.e. that it was more common in the educated and professional classes, and that it resulted largely from environmental factors which caused subtle and undetectable alterations in neurochemistry (Demitrack & Greden, 1991; Wessely 1990). Doctors in particular, were apparently vulnerable to the illness, with Wessely reporting that they formed 10% of Beards' patients. Beard himself was reportedly a sufferer of the illness and there are some claims that much of his theory was derived from an attempt to explain his own symptomatology (ibid).

Soon after publication of *American Nervousness*, DaCosta described a similar syndrome of fatigue, breathlessness, palpitations, dizziness, chest pain, headache, digestive disturbances and sleep difficulties in a group of battle-weary soldiers during the American Civil War (Greenberg, 1990). This "effort" syndrome was apparently precipitated by febrile illnesses, gastroenteritis, and severe exhaustion. Cardiac abnormalities were also thought to be associated with the condition. After conducting extensive examinations which included autopsies, DaCosta concluded that the syndrome revealed "the connection between functional derangement and organic change" (as cited in Straus, 1991, p. 3). It appears that DaCosta's syndrome had a high incidence during World War I, with approximately 60,000 cases being recorded. Of these cases, over two thirds received medical pensions (ibid). Subsequent examination of DaCosta's syndrome by medical specialists during the earlier half of this century, rejected the idea of a somatic basis for the illness. Laboratory experiments in which fatigued subjects were investigated using treadmills and exercise cycles, could find no clear relationship between normal fatigue, recovery and lactic acid accumulation (Greenberg, 1990). Failure to demonstrate an organic basis for fatigue led Wood in 1941 to argue that the "effort" syndrome should be viewed as a psychoneurosis that was etiologically rooted in childhood and family history (as cited in Straus, 1991). This view of fatigue as having an emotional rather than physical basis, was popularly held in the early 1900's (Greenberg, 1990).

The diagnosis of neurasthenia as a descriptor for poorly defined fatigue was apparently short-lived (Wessely, 1990). One possible explanation was the growth of psychiatry as a profession, with the subsequent introduction of new terminology; for example, terms like

depression, hysteria, neurosis, and obsessive compulsive disorders, were used to describe what had formerly been referred to as neurasthenia. Freud apparently discarded neurasthenia in favour of anxiety neurosis and hysteria (Wessely, 1990). According to Freud, neurasthenia was characterized by headaches, spinal irritation, and abdominal discomfort, and was caused by excessive masturbation and spontaneous seminal emissions (ibid). A second reason for the decline of neurasthenia was the lack of concrete evidence for a neuropathological component of the illness, and subsequent disinterest when it became evident that it did not fit neatly into a simple medical model in terms of diagnosis, etiology and treatment. According to Wessely, this led to the subsequent abandonment of the concept of neurasthenia by the neurological profession. A final reason for "neurasthenia" losing its appeal, was increased recognition that it was more widespread in the lower social classes than had been previously acknowledged; as a result, the label lost its status as a disease of the wealthy (ibid). Nevertheless, old concepts die slowly, and according to Demitrack and Greden (1991), the label of neurasthenia has not been abandoned entirely; it still appears in the International Classification of Disease (ICD-10) and is apparently a common diagnosis in China and India (Wessely, 1991a).

The question of whether neurasthenia was the precursor of modern day CFS warrants a mention since it is widely acknowledged that the two syndromes bear a striking similarity in presentation (Greenberg, 1990; Shorter, 1993; Straus, 1991; Wessely, 1990, 1991a;). The exact incidence and clinical heterogeneity in early research studies is, however, not well established; Shorter (1993) cautions that neurasthenia is too vague a label to be directly equated with chronic fatigue syndrome. Furthermore, he suggests that due to the lack of sophisticated diagnostic and examination procedures in the last century, many individuals with legitimate physical illness were probably diagnosed as neurasthenic. Wessely (1990) and Greenberg (1990) seem more willing to make a direct comparison between modern day chronic fatigue syndrome and neurasthenia. In support of his argument, Wessely cites as evidence the findings of an association between infectious illnesses (e.g influenza) and neurasthenia at the end of the last century. He also suggests that at the turn of the century, physiological opinion suggested an interaction between neurasthenia, infection and "mental stress". This interaction has formed the basis of more recent debate on the nature of chronic fatigue syndrome.

1.1.2 The "Second Wave"

The present day precursors of chronic fatigue syndrome can be more reliably traced to various events that occurred subsequent to 1934. Although this section is subdivided in terms of specific events that took place, it should be noted that there is substantial symptom overlap between designations such as neuromyasthenia, myalgic encephalomyelitis, Iceland Disease, Royal Free Hospital disease and Addington disease, and that these various names primarily reflect the geographical locations of occurrence. Although most of these outbreaks were reported from the USA, epidemics were also reported as occurring in England, Iceland, Denmark, Germany, Australia, Greece and South Africa (Shafran, 1991). There is some agreement that these outbreaks of illness (characterized by chronic fatigue) may be collectively referred to as the "second wave" (Shorter, 1993; Thomas, 1993). Consistency of symptoms appears to be a characteristic of these outbreaks; in this regard, Briggs and Levine (1994) note that:

> the majority of cases in each outbreak are heralded by a viral-like illness that is followed by a clinical course of excessive fatigue, headaches, myalgias, low-grade fevers, and other systemic symptoms occurring together with a wide range of neurological features (p. 32).

During this century, the first epidemic of an illness characterized by fatigue occurred in 1934 when 198 employees of the Los Angeles County General Hospital fell ill with symptoms of fever, muscle pain/weakness, headaches and fatigue. Excessive sweating or abnormal dryness of the skin, coldness, cyanosis and brittle nails were also commonly reported, while inflammation of the joints occurred in a third of adult cases (Jenkins, 1991). Similar symptoms occurred at several neighbouring hospitals, and the illness (which was of unknown etiology) came to be known as "epidemic neuromyasthenia" (Shaffran, 1991). Particular features of the epidemic included mildness of attack, marked degree of muscle weakness, unusual communicability (i.e. contagion), a seasonal peak (June), and protracted recovery in adults. For example, out of 100 cases, 35 still had muscle weakness at a 12 month follow-up (Jenkins, 1991). Subsequent, similar outbreaks of this "neuromyasthenia" were reported at different geographical locations between 1934 and 1958. Although it initially appeared that outbreaks were specific to hospital

settings and primarily affected health care professionals and patients, it soon became evident that the broader community was also vulnerable.

One such occurrence in Iceland in 1948 has been variously referred to as Icelandic Disease or Akureyri Disease. Hyde reports that 476 people fell ill with a disease characterized by fatigue, muscle pain, muscle weakness and neurological complaints. Women seemed to be more vulnerable than men although the sex ratio was equal below the age of 20. There was a low incidence in childhood and the elderly, with maximal incidence in the 15-19 years age range (as cited in Jenkins, 1991). The medical experts on the island were somewhat baffled by the variable symptomatology, and also because the affected patients appeared to experience tiredness which was out of all proportion to their illness. Viral studies failed to implicate known viral etiological agents or poliomyelitis; as a result, doctors eventually settled on hysterical paralysis as the preferred diagnosis. A follow-up study by Sigurdsson and Gudmundsson in 1956 revealed that only 25% of the more severely affected, and 43% of the mildly affected patients, had made a full recovery (as cited in Jenkins, 1991).

A few months after the 1948 Icelandic epidemic, an epidemic of apparent poliomyelitis occurred in Adelaide (Australia). By 1951, 800 patients were symptomatic with an illness characterized by headache, stiff back, aching limbs, pain behind the eyes, upper respiratory tract infection, mild muscle weakness and fever. Jenkins (1991) reports that although the condition in the early stages was indistinguishable from poliomyelitis, the delayed recovery in some of the patients (highlighted by persistent muscle aching and weakness, irritability, lack of concentration and emotional stability) was inconsistent with a diagnosis of poliomyelitis. A similar conclusion was reached following a 1950 outbreak of what initially appeared to be poliomyelitis in New York State (ibid). Further outbreaks of similar epidemics appeared in Denmark and in England during 1953 and 1954. Jenkins reports that in all of these outbreaks, virological tests for poliomyelitis were inconclusive, whereas tests for Coxsackie and mumps were found to be negative.

One of the "second wave" outbreaks which has been extensively documented, occurred at the Royal Free Hospital in London in 1955. The outbreak started in July when a resident doctor

and a ward sister were admitted as patients with what was considered to be an obscure illness. Within 15 days, more than 70 staff members were affected. Subsequently, a total number of 292 staff members experienced symptoms of sore throat, headache, stiff neck, blurred vision, low grade fever, and swollen glands. After a few days, the illness progressed to one of myalgia, apathy, fatigue, and depression. Although involvement of the central nervous system was not disputed in the early stages (hence the name encephalomyelitis), subsequent investigations of the cerebrospinal fluid failed to reveal a viral cause for the ongoing symptomatology. Shorter (1993) mentions that the illness was renamed the following year as "benign encephalomyelitis" since nobody actually died from it, although the term "benign" was later dropped in recognition that the patients experienced nothing benign about their symptoms. Subsequent sporadic outbreaks with similar symptoms were described as myalgic encephalomyelitis or ME.

A difference of opinion about the etiological nature of the Royal Free outbreak is apparent. The impression of doctors who were affected was that they had been infected by a viral encephalitis that was highly contagious. Dawson (1987) reports that fever was apparent in 89% of cases, lymphadenopathy in 79%, ocular palsy in 43%, and facial palsy in 19% of those studied. However, subsequent psychiatric re-analysis of the patient records in 1970 by McEvedy and Beard, reinforced the notion of a functional disorder (i.e. that the contagion was not due to an organic illness, but rather represented a kind of mass hysteria or psychoneurosis [as cited in Wessely 1991a]). This opinion was disputed by Ramsay (1978) who emphasized the endemic nature of the disease in an epidemiological investigation of similar sporadic cases seen over a widely dispersed geographical region. These divergent viewpoints have still not been successfully resolved; reviewers such as Thomas (1993) maintain that the Royal Free outbreak represented an epidemic of mass conversion hysteria, possibly triggered by post-infective encephalomyelitis in a small number of cases. In contrast, Jenkins (1991) and Henderson (1994) emphasise the organic nature of the outbreak.

Further smaller outbreaks of epidemic neuromyasthenia occurred in Maryland (USA) in 1953; at Middlesex Hospital (England) in 1954; in Leon County (USA) in 1954; in Dalston (Cumbria) in 1955; at Addington Hospital (Durban) in 1955; in North Finchley (England) in 1964; and at the Hospital for Sick Children (Ormond Street, London) in 1970. Although

apparently not well documented in the medical literature, numerous other outbreaks (possibly in excess of 60 cases), have been reported since 1934 (Levine, 1994).

Of local interest, is the outbreak of an illness resembling poliomyelitis which occurred at Addington Hospital (Durban) in 1955. Fifty-nine nurses were affected in the first week, with a further thirty-nine becoming affected in the following few days (Hill, Cheetham, & Wallace, 1959). Occipital headache, lassitude, sore throat, burning eyes, nausea and vomiting, and severe backache were the most common presenting complaints in the prodromal phase (lasting up to 14 days). This was followed by an acute phase characterized by parasthesia, muscle pain, and an inability to sit unaided in almost all cases. Convalescence proceeded over three months for the majority, although relapses were common with symptoms persisting for up to nine months in some cases. Incomplete recovery was apparent in 11 cases at a three year follow-up (ibid). Medical examination found evidence of a low grade fever and various neurological symptoms in the majority of affected individuals, while audiograms revealed transient nerve deafness. Although haematological and viral investigations were negative, toxicological studies provided evidence of an unidentified toxic substance in some cases. Emotional lability (hysteria) and neuropsychological deficits (poor concentration and defective memory) were also apparent in the majority of cases. Although an etiologic agent was never identified by the Addington doctors, an infectious encephalomyelitis was suspected. In a recent review of this outbreak, Briggs and Levine (1994) comment that the Addington report, because of the severe neurological involvement, became a prototype for use of the term "myalgic encephalomyelitis".

In all of the outbreaks reviewed so far, a symptom cluster is evident to a greater or lesser extent. The symptoms included dizziness, headache, lethargy, drowsiness, sleep disturbance, blurred vision, muscle pain and weakness, exercise-induced muscle fatigue, enlarged lymph glands, low grade fever and depression. In virtually all cases, other illnesses considered in the differential diagnosis were excluded on the basis of clinical and laboratory examination. In at least one outbreak, the clinical picture was thought to resemble Coxsackie or echo virus infection, although virological examination could not confirm this (Jenkins, 1991). In this context however, it may be important to note that sophisticated serologic tests were not in general clinical use until the mid 1970's (Shafran, 1991). An additional consideration highlighted by Henderson (1994),

is the possibility that by the time the symptoms had developed and the patient sought medical help, the etiologic agent may no longer have been detectable. Nevertheless, the presence of subtle differences in neurological and clinical presentation of 12 outbreaks reviewed by Briggs and Levine (1994), suggested the presence of more than one etiological agent.

A prominent differential diagnosis in many of the early outbreaks was acute poliomyelitis, abortive poliomyelitis, or poliomyelitis suspect. This tended to give some weight to an organic etiological agent. However, these epidemic cases differed from poliomyelitis in that muscle aching, pain, and tenderness were the prominent features throughout the course of the illness, and were not accompanied by the extreme muscle weakness and wasting normally seen in poliomyelitis (Jenkins, 1991). Furthermore, electromyographic studies conducted on some of the Royal Free patients failed to reveal any involvement of the anterior horn cells in the spinal cord, as might be expected in poliomyelitis (Shepard, 1989). To add to the etiological confusion was an outbreak of confirmed poliomyelitis in Iceland a few years after the Akureyri epidemic. The residents of Akureyri were not significantly affected by this, a finding which has been interpreted as indicating possible immunity (Jenkins, 1991). Furthermore, the children who had been exposed to the earlier outbreak, responded to the poliomyelitis vaccination with a profile that suggested previous exposure to an agent which was immunologically similar to poliomyelitis virus (ibid).

While the presentation thus far presents some of the well-documented epidemic cases, it is important to note that more isolated and sporadic single cases (i.e. endemic cases) also appear in the literature. Some of these cases are reviewed by Jenkins (1991), and are remarkable only from the standpoint of similarity in symptomatology to the larger epidemics. On the other hand, Levine (1994) suggests that the lack of a case definition prior to 1988, limits the level of comparison that can be made. From an etiological standpoint, the history of CFS prior to 1980 reveals some attempts to explain the symptoms of chronic fatigue on the basis of various environmental, metabolic, infectious, immunologic and psychiatric disturbances. Some of the popular explanations included brucellosis, influenza epidemics, and hypoglycemia; however, none of these diagnostic labels were sufficient to explain all of the symptoms.

1.1.3 Recent History (1978-1988)

The outbreaks of epidemic myalgic encephalomyelitis reviewed above, eventually culminated in an international symposium hosted by the Royal Society of Medicine in Britain, in 1978. It is noted that interest groups had already been in existence for some time prior to this symposium; for example, the Myalgic Encephalitis Study Group was formed in Britain in 1975. Nevertheless, the aim of the symposium was to arrive at some consensus about the condition, and three conclusions about ME were reached: (1) it is a specific disease entity; (2) it is of unspecified viral origin; and (3) it is not psychogenic. Nevertheless, consensus was not reached at this symposium and some experts apparently disagreed with all three conclusions (May et al., 1980). The lack of agreement led to continued controversy about the nature of the illness and gave rise to a number of investigative studies during the 1980's. These later studies differed from the earlier ones in their more comprehensive selection of investigative techniques.

May et al. (1980) reported on an outbreak of ME that occurred at a school in Britain in 1979. The outbreak affected 45 of 103 female residential pupils, and was characterized by headache, sore throat, abdominal pain, tiredness, weakness, pallor and tearfulness. The symptoms in many cases were severe and recurrent, lasting up to eight weeks. Medical assessment included microbiological and virological tests, while a limited psychological assessment was also included (Eysenck Personality Questionnaire). Results failed to demonstrate a convincing neurological or viral basis for the delayed recovery, although late recoverers were identified as having comparatively more psychological symptoms. The authors appealed for future studies to consider psychological factors in the pathogenesis of delayed recovery.

In 1983, Keighley and Bell published evidence of elevated Coxsackie B titres in 16 of 20 patients presenting with ME at their Scottish practice between 1981 and 1982. The presenting picture common to nearly all cases was a non-specific one of malaise, tiredness, and exhaustion following physical or mental effort. Anxiety and/or depression was also noted in the majority of cases. The raised antibody titres to Coxsackie infection were interpreted as evidence of a recent infection. A more extensive study was conducted by Behan et al. (1985); it involved the use of

clinical, pathological, electrophysiological, immunological and virological methods. Evidence from 50 patients with CFS was strongly supportive of an organic etiology (i.e. a link was established between fatigue and Coxsackie virus infection). Findings included abnormal muscle metabolism, reduced levels of lymphocytes, and high levels of antibodies to Coxsackie B viruses. The authors concluded that the syndrome was due to immune system dysregulation and persistent viral infection.

The Epstein-Barr virus (EBV) and human herpesvirus 6 (HHV-6) were implicated in a series of outbreaks of CFS occurring in northern Nevada between 1984 and 1988. Although estimates of more than 400 affected patients were made by the treating physicians, only the more severely affected patients ($n = 20$) were selected for extensive study by Daugherty et al. (1991). Clinical characteristics of these patients are summarized in Table 1-1.

Table 1-1. Clinical Characteristics Observed in 20 Patients with Severe CFS

Acute onset of influenza-like symptoms, including myalgia, with subsequent extreme fatigue of several months duration.
Recurrent upper respiratory tract infection (URTI).
Tender, enlarged lymph nodes.
Night sweats and/or low grade fever.
Neuropsychological abnormalities (particularly concentration and memory difficulty).
Absence of evidence for endocrine, neoplastic, or collagen vascular disease.

(Dougherty et al., 1991, p. 40)

Another research group working in the same geographical area, conducted an extensive three-year follow-up study of patients affected by four clusters of the chronic fatigue syndrome between 1986 and 1989 (Levine et al., 1992). In contrast to the viral etiologies suggested by Dougherty et al. (1991), none of the viruses investigated could be etiologically linked to the outbreaks. However Levine and colleagues could not rule out the possibility that undetected viruses were responsible. The results of this study were useful in the generation of a clinical case

definition for the Nevada outbreaks. This definition included the following criteria: (a) severe persisting fatigue following an acute illness appearing in an individual who was premorbidly asymptomatic in terms of physical or psychological symptoms; (b) presenting signs and symptoms of an acute infection including sore throat and/or lymphadenopathy; (c) severe and persistent headache and/or myalgias; and (d) abrupt change in cognitive function or the appearance of a new mood disorder.

In consolidating the research findings leading up to the publication of the 1988 CDC criteria for CFS, a number of conclusions can be drawn:

(1) Firstly, the symptoms associated with chronic fatigue syndrome are not new; evidence from the medical literature indicates that syndromes characterized by fatigue were described as far back as end of the 18th century. To this extent, it appears that current conceptualizations of CFS are derived not only from the more recent studies but also from accounts of earlier epidemics.

(2) Despite the various terms used to describe chronic fatigue syndrome, certain core symptoms are common. These include fatigue and lethargy, tiredness, muscle pain and an absence of a distinct organic etiology.

(3) CFS may occur in both an endemic and epidemic form. An endemic form implies that the illness is contracted independently of the normal pathways for viral or bacterial transmission of illness. An epidemic transmission route implies an infectious disease process. However, the etiological agents responsible for these two forms of CFS may be different (Komaroff & Buchwald, 1991). A viral etiology is suggested in at least some of the more recent epidemics of chronic fatigue syndrome; the commonly implicated agents are the Epstein-Barr virus (EBV), Coxsackie B viruses and human herpesvirus 6 (HHV-6). Concurrent or pre-existing psychological symptoms are also apparent in many of the epidemics and are implicated in the course of the illness.

(4) Although studies leading up to 1988 place the concept of CFS within a useful

historical and social perspective, they also highlight the controversial nature of the illness (in terms of nature, cause and outcome).

To elaborate on this last point, one of the difficulties in understanding CFS is that it is a syndrome or collection of different symptoms that shares an overlap with other conditions. The etiology is uncertain and no single pathological process has been identified. However, this phenomenon is not new to medicine; according to Shorter (1993) many illnesses which are with us today (such as multiple sclerosis) were also controversial until aspects of the disease process had been fully understood. Komaroff (1993) makes the observation that acceptance of an illness by the medical profession is dependent on the presence of verifiable abnormalities. Thus even though a disease process may be obscure in terms of varied presentation or lack of definitive etiology, acceptance is maximised by the presence of objective abnormalities. Unfortunately, CFS falls short of the mark in this regard.

1.1.4 Case Definitions (1988-1991)

Despite the various precursors of chronic fatigue syndrome, there is now some agreement on the clinical presentation. However, this was not always the case; frustration and dissatisfaction with the lack of diagnostic criteria prior to the publication of the Centers for Disease Control (CDC) criteria was expressed (Church, 1980; Gordon, 1988). David, Wessely, and Pelosi (1988) suggested that two main diagnostic features could be identified in patients suffering from postviral fatigue syndrome; fatigue and emotional disturbance. The importance of the inclusion of both organic and functional (psychological) factors, the use of control groups in research studies, and a request for well-structured epidemiological studies was emphasized by Gordon (1988). Hughson (1988) was one of the first to call for recognition of a syndrome with wider inclusion criteria than just a recognised viral etiology. In Australia, Lloyd, Wakefield, Boughton, and Dwyer (1988) complained that descriptors such as postviral fatigue syndrome and myalgic encephalomyelitis were too restrictive and contaminated by negative connotations associated with their history. These researchers assembled their own diagnostic criteria (Lloyd, Phales, &

Gandevia, 1988) and published them a few months ahead of the CDC criteria (see Table 1-2).

Table 1-2. Operational Criteria for CFS as Proposed by Lloyd, Phales, et al. (1988)

Chronic, persistent or relapsing generalized fatigue causing disruption of usual daily activities and present for at least 6 months: plus two major criteria or one major and three minor criteria (symptoms, signs, or assessment):

1. *Symptoms*: present for 6 months or on 3 or more occasions
   (a) Major: generalized exercise-induced muscle fatigue at low* workload.
   (b) Minor: myalgia, arthralgia, depression, tinnitus, parasthesia, headaches, concentration/ memory impairment

2. *Signs:* present on at least one occasion subsequent to the initial illness:
   (a) Major: lymphadenopathy
   (b) Minor: pharyngitis, muscle tenderness

3. *Immunological assessment:*
   (a) Major: cutaneous anergy, T4 or T8 lymphopenia
   (b) Minor: hypoergy

* Exercise must be limited by fatigue (not pain) and must occur at a workload considerably less than that easily achieved shortly prior to the onset of the disease.

(reproduced from Lloyd, Phales, et al., 1988, p. 1317).

Although comparable to the later CDC criteria, greater emphasis was placed on neuropsychological complaints. Despite the appeal of the Australian criteria (in terms of simplicity), it appears that the efforts of Lloyd and his colleagues were largely upstaged by the U.S government-backed CDC efforts, the result being that their recommended criteria have not seen much use outside of Australia. A parallel attempt at case definition was also published by Ramsay (1988). His criteria were somewhat less specific, and consisted of three criteria: (i) muscle fatigability following relatively minor exertion, and lasting three or more days; (ii) remarkable variability and fluctuations of symptoms; and (iii) alarming chronicity.

Frustration over the lack of definition of CFS was experienced not only by the medical profession, but by patients themselves. Autobiographical accounts and media coverage began to

appear in the popular press (Beechey, 1989; Cowley, Hager, & Joseph, 1990; Seligman, Abramson, Shapiro, Gosnell, & Hager, 1986) as well as in the medical literature (Church, 1980; Harvey, 1989). The latter half of the 1980's saw the formation of patient support groups in numerous parts of the world and Spracklen (1988) reports that the issue of CFS was even brought before the British Parliament in early 1988. This was done in an apparent attempt to draw public attention to the plight of afflicted individuals and to call for progress to be made in the causes, effects and treatment of CFS. Wessely and Powell (1989) maintain that in 1988, the ME Association had become Britain's fastest growing charity. These latter events had been preceded by a meeting of an informal investigational working group from the Division of Viral Disease (Centers for Disease Control) in April 1987; their aim was to arrive at a tentative consensus for the clinical features of CFS. Their subsequent publication in 1988 proposed a definition of chronic fatigue syndrome that could be "the basis for conducting future epidemiologic and clinical studies" (Holmes et al., 1988, p. 388). The CDC criteria are summarized in Table 1-3.

The extent to which these criteria are fulfilled by patients presenting with chronic fatigue varies from study to study. Klonoff (1992) reports that prevalence rates range from 19-30%, although Schluederberg et al. (1992) suggest a slightly wider range of 25-66%. An unpublished CDC study conducted in 1991 (as cited in Klonoff, 1992) found that 26% of referred patients met the criteria although another 15% failed to meet all eight required minor criteria. The remaining 59% of cases had an underlying organic or psychological condition that accounted for the fatigue. According to Boegman (1995), one recent unpublished North American study by Buchwald contrasted the prevalence of CFS and chronic fatigue, and found that CFS accounted for only a small proportion of fatigued patients (chronic fatigue ± 5,000 per 100,000; CFS ± 250 per 100,000). One of the local South African experts on CFS (Professor Allan Smith, Department of Virology, University of Natal Medical School, Durban) maintains that of the 540 fatigued patients he has studied, roughly 66% met the CDC criteria (personal communication, April 1994). Another local practitioner and CFS expert (Dr. Ray Moore) reports that approximately 40% of the 500 fatigued patients who have consulted him since the mid 80's, meet the CDC criteria (personal communication, April 1994). The remainder fulfil one of the differential diagnoses (such as fibromyalgia), although he is of the impression that considerable overlap exists with depression. A similar figure of 40% of cases meeting the CDC criteria is reported by Bell (1994).

Table 1-3. CDC Diagnostic Criteria for Chronic Fatigue Syndrome

For diagnosis, both major criteria must be present, plus the following minor criteria: (1) at least 6 symptoms and at least 2 physical signs; or (2) at least 8 of 11 symptoms.

Major criteria

1. New-onset of fatigue lasting longer than 6 months and that is severe enough to reduce daily activity below 50% of premorbid level.
2. Exclusion of medical or psychiatric conditions that could account for the symptoms.

Minor criteria:

Symptoms (must have begun at or after the time of onset and have persisted or recurred for at least 6 months).

1. Low-grade fever.
2. Sore throat.
3. Painful lymph nodes.
4. Generalized muscle weakness.
5. Muscle discomfort or myalgia.
6. Exercise-induced fatigue lasting longer than 24 hours.
7. Generalized headaches.
8. Migratory arthralgias.
9. Sleep disturbance (hypersomnia or insomnia).
10. Neuropsychological complaints (one or more of the following: photophobia, visual scotomas, forgetfulness, irritability, confusion, difficulty concentrating, depression).
11. Description of main symptom complex as having developed over a few hours to a few days.

Physical signs:

Medically documented on at least two occasions, at least one month apart.

1. Low-grade fever (37.5 degrees C to 38.6 degrees C).
2. Nonexudative pharyngitis.
3. Tender anterior or posterior cervical or axillary lymph nodes.

(reproduced from Holmes et al., 1988, pp. 388-389).

duration of six months from onset of the illness must have passed before a diagnosis can be made. One recent study has shown that there is no difference in prognosis between patients who have been ill for longer than 6 months, and those with shorter histories (Sharpe, Hawton, Seagroatt, & Pasvol, 1992). This casts some doubt on the usefulness of elapsed time as a diagnostic criterion. Other complaints centre around problems of definition and the restrictive nature of the criteria. For example, Manu, Mathews, and Lane (1988) found that 95% of 135 consecutive patients who attended a fatigue clinic in a university hospital with at least a six month history of debilitating fatigue, failed to meet CDC criteria on the basis of concurrent depression. Kroenke (1991) comments that nearly 70% of CFS patients fail to meet research criteria on this basis, while Hickie, Lloyd, Wakefield, and Parker (1990) also note that the CDC criteria effectively exclude a large number of patients with psychiatric disorders.

Complaints that both the CDC and Australian criteria were unsatisfactory in practice, were voiced by a number of clinicians (David et al., 1988; Sharpe et al., 1991). The efficacy of the CDC case definition in assessing borderline diagnostic cases is questioned by Schluederberg et al. (1992), and Komaroff and Buchwald (1991). The latter suggest that there are virtually no differences between patients who fulfill and those who don't fulfill the case definition in terms of demographic features, symptoms, signs and laboratory test results. Other difficulties noted by Fukuda et al. (1994) include the observation that the case definition is often modified in practice because of problems in interpreting or applying some of the criteria.

The adequacy of the 1988 CDC criteria was investigated in a prospective study by Komaroff (1996) in which clinical and laboratory data was collected from 281 CFS patients, 311 healthy controls and two additional comparison groups of multiple sclerosis (n = 25) and depressed patients (n = 19). The results showed that the CDC minor criteria symptoms were able to distinguish patients with debilitating chronic fatigue from healthy control subjects, while many distinguished the CFS patients from the MS and depressed comparison groups.[1] Two additional symptoms not currently part of the CDC criteria (anorexia and nausea), were found to discriminate the CFS patients from the control and comparison groups; the authors felt that inclusion of these

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1 The discriminating symptoms included myalgias, post-exertional malaise, headaches, chronic fever and chills, and swollen glands in the neck or underarm.

symptoms would strengthen the CDC criteria. Likewise, it was felt that the elimination of three symptoms (muscle weakness, arthralgias, and sleep disturbance) would also improve the CDC case definition of CFS.

It is evident then, that dissatisfaction remained after the Centers for Disease Control published their diagnostic criteria (although in fairness, it is noted that the CDC published their criteria as a "working" case definition, implying that it was an interim measure pending further development). Furthermore, the CDC criteria were developed for research purpose rather than being aimed at clinicians in practice (Schluederberg et al., 1992). Simon Wessely (one of the leading figures in the psychiatric study of CFS) published a cautionary article "*Myalgic Encephalomyelitis - a warning*" shortly after the appearance of the CDC criteria. In his paper, he highlighted the difficulties of defining postviral fatigue, lack of operational criteria, inadequate diagnostic precision by clinicians referring patients for further investigation, and insufficient attention to methodological detail in research studies (Wessely, 1989). Fortunately, U.S. government backing for continued research into CFS was forthcoming, and the CDC was awarded $1.18 million for ongoing research and surveillance of the syndrome (Harvey, 1989). Nevertheless, it was a further 6 years (i.e. 1994) before the original CDC criteria were revised (see section 1.6). In the meantime, British researchers examined the shortcomings of the CDC criteria and proposed their own revision in 1991 (Sharpe et al., 1991). The British revision was based on a consensus meeting held in Oxford in March 1990; it was attended by physicians, virologists, neurologists, psychiatrists, psychologists, and various scientists with an interest in the field of CFS. The aim of the meeting was to "seek agreement amongst research workers on recommendations for the conduct and reporting of future studies of patients with chronic fatigue" (Sharpe et al. 1991, p. 119). Although the diagnostic criteria were perhaps not as rigorous as those proposed by the CDC, the advantage of the so-called "Oxford" or British criteria lies in the attention to the definitions of the various symptoms and signs associated with CFS. The Oxford criteria are summarized in Table 1-4.

Table 1-4. Research Diagnostic Criteria for CFS (Sharpe et al., 1991)

Two broad syndromes are defined: 1. Chronic fatigue syndrome (CFS)
2. Post-infectious fatigue syndrome (PIFS)

1. Chronic fatigue syndrome (CFS)

(a) a syndrome characterized by fatigue as the principal symptom,

(b) a syndrome of definite onset that is not life long,

(c) the fatigue is severe, disabling, and affects physical and mental functioning,

(d) fatigue should have been present for a minimum of six months during which it was present for more than 50% of the time

(e) other symptoms may be present, particularly myalgia, mood and sleep disorders

(f) conditions to be excluded include medical illnesses which are known to produce fatigue, schizophrenia, bipolar affective disorders, substance abuse, eating disorders and proven organic brain disorders

2. Post-infectious fatigue syndrome (PIFS)

This is a subtype of CFS which either follows an infection or is associated with a current infection. To meet research criteria for PIFS patients must fulfill the criteria for CFS (1), and fulfill the additional criteria of:

(a) definite evidence of infection at onset or time of presentation and which is corroborated by laboratory evidence,

(b) the syndrome is present for a minimum of six months after onset of infection

(adapted from Sharpe et al., 1991).

In contrasting the CDC, Oxford and Australian case definitions, the major differences appear to be that only the Oxford criteria require a definite onset of the illness, only the Australian criteria require the presence of post-exertional fatigue, and only the CDC criteria require a specified number of multiple minor symptoms and signs. The comparability of these three systems was recently evaluated in a study by Bates et al. (1994). A large number of fatigued patients were classified according to whether they met one or more of these case definitions. Of the 805 patients studied in three consecutive evaluations, 61% met the CDC criteria, 55% met the Oxford criteria, and 56% fulfilled the Australian criteria. These figures suggest relative diagnostic

similarity of the three case definitions. However, the study also revealed that small changes in case definition changed these figures considerably. For example, if patients without post-exertional fatigue had been included, the figures fulfilling the Australian criteria would have risen from 56% to 70%. Despite these findings, some variability (in terms of the number of patients who actually meet diagnostic criteria), exists in the literature. For example, McDonald, David, Pelosi, and Mann (1993) found that only 17 (26%) of 77 fatigued patients met the British criteria for CFS (a further 12.5% were sufficiently fatigued but excluded on the grounds of uncertain onset and concurrent psychiatric disorder). Goudsmit (1994) suggests that the three diagnostic systems are differentially sensitive to the prevalence of fatigue and that a failure to recognize this can lead to inappropriate treatment interventions. Thus, prior to the 1994 revision of the CDC criteria, there appears to have been incomplete agreement about the comparability of the three diagnostic systems reviewed above.

1.2 CLINICAL PRESENTATION OF CFS

1.2.1 Diagnostic Difficulties

The central feature of CFS is disabling fatigue and exhaustion. However, fatigue is a common complaint of patients who present at a general medical practice; indeed, it has been estimated that fatigue accounts for an estimated 6-10 million medical consultations a year in the United States, with a cost liability in the region of $1 billion (Klonoff, 1992; Kroenke, 1991; Manu et al., 1989). In the UK, a questionnaire survey of 611 general practice attenders found that 10.2% of men and 10.6% of women had experienced substantial fatigue for a minimum duration of one month (David et al., 1990); attributes included physical, psychological, and social stress, although it is interesting to note that physical ill-health (including viral infection) was associated with more severe fatigue. This latter finding is however not consistently reported in the literature; for example, a recent American study examining fatigue in HIV-infected individuals failed to find any significant association between fatigue measures and physical illness parameters (O'Dell, Meighen, & Riggs, 1996). Other research seeking to evaluate the incidence of chronic fatigue in primary care attenders, includes the study by McDonald, David, et al. (1993) in which a 77 of 686 patients were identified as having chronic fatigue (as measured by a fatigue questionnaire). These patients were subsequently given a psychological, social and physical evaluation; the results indicated a high incidence of psychiatric comorbidity (52 of 77 cases). Sex differences in fatigue complaints have been reported, with prevalence studies suggesting an average of 19.4% of males and 25.2% of females (Katon & Walker, 1993).

It seems reasonable to suggest that on account of the human condition, virtually everyone will, at some stage during the course of their lives, experience a degree of fatigue that may not be readily attributed to intellectual, emotional or physical antecedents. The diagnostic challenge lies in identifying those patients who have fatigue associated with CFS, from those whose fatigue may be attributable to other factors such as psychiatric illness and/or organic illness. The separation of psychological from organic factors is not easily done; Gulledge (1991) notes that both fatigue and depression are integral symptoms of a wide array of medical disorders. One of the challenges for medical practitioners and researchers alike is the difficulty in distinguishing the cause and

effects of fatigue; for example, is fatigue a symptom of depression, is depression a consequence of fatigue, or is depression an integral part of CFS? Adding to the diagnostic difficulty, is the finding that fatigue comprises the *most severe* symptom in only about half of CFS patients according to Bell (1994); the remainder may have headache, myalgia, emotional changes, or neurocognitive complaints as the most severe symptoms. In addition, symptom variability (in terms of extent and severity) appears to be a prominent characteristic of CFS (ibid).

A related diagnostic complication is that the other features of CFS, such as sore throat, headache, myalgias, cognitive failure and sleep disruption, are also experienced in varying degrees by most people at some point in their lives. However, the presence of these symptoms does not necessarily imply a pathological state. The challenge for the diagnostician is determining the point at which fatigue and the heterogeneous symptoms associated with CFS become a pathological illness. To make the diagnosis, other differentials must be excluded (see section 1.2.6); however this is not always a straightforward task according to Komaroff (1993). Case studies provided by McDonald, David, et al. (1993) illustrate this diagnostic challenge:

> *CASE # 1 - Fatigue due to dysfunctional lifestyle:*
>
> A 20-year-old single Irish student nurse living in London for last 1½ years. Her fatigue started when she came to London but while most other students complained of fatigue at the beginning of their training only, she reports persistent fatigue. She enjoys work and gets on with other staff. She complained that the fatigue made it hard for her to cook for herself and to socialise. Her lifestyle was restricted. She seldom goes out, staying in the nurses' home watching videos. She said she never felt so tired and cannot explain it. She often worries about her health. She denied being depressed but complained of irritability and occasional poor concentration. She had normal birth and development. Her parents were strict but she had a happy childhood and schooling. She often worked after school to earn extra pocket money. She has had boyfriends since the age of 16 but none since moving to London. She has had irritable bowel syndrome for two years. Case # 1 has six siblings. Her father is a community nurse. The patient described

having a good relationship with her parents. (ICD 9 diagnosis = neurasthenia)

CASE # 2:

A 33-year-old married physiotherapist who has complained of fatigue for 4 years. Problems around the time of presentation were backache and infertility. She believes her chronic backache to be due to her work and that it was made worse by feeling "stressed". She worries about her back and the pain keeps her awake sometimes. No abnormality has been found on X-ray or CT scan of her spine. She has been unable to conceive for six years. Her husband has a low sperm count. They have had two failures at *in vitro* fertilisation and were about to start a third. The IVF programme is highly stressful for the couple. The fatigue is continuous and makes it necessary for the patient to lie down during the day. She complains of poor concentration and feels low sometimes when she thinks about her problems. She was a premature baby and was shy and nervous as a child. She also had a stutter. She did well at school academically but found it hard to mix with her peers. After school she trained as a physiotherapist. She has worked part-time for the past two years. Of note in the family background is a clash of personalities between the patient and her mother who had infertility and backache. The patient is an only child and was born after numerous miscarriages and a stillbirth. (ICD-9 diagnosis = neurotic depression).

(McDonald, David, et al., p. 997).

For many patients, CFS is a diagnosis based on clinical history and exclusion of other illnesses known to give rise to similar fatigued states. Mechanic (1993) notes that the exclusionary possibilities are numerous, often involve expensive laboratory tests, and that the level of investigation is largely determined by factors such as the patient's illness behaviour, resource availability, and finance. An additional determinant not mentioned by Mechanic, is the interest and competence of the medical practitioner (many of the participants in the current study complained of being disappointed at the extent of the work-up offered by the medical profession).

In some cases, the diagnostic process is determined by employment setting; in this regard, Mechanic makes the interesting observation that American doctors are more likely to pursue even remote clinical possibilities, and to use more invasive diagnostic procedures than their British counterparts. The reason for this, according to Mechanic, is that British doctors tend to be employed on a salaried basis, whereas American doctors are usually paid according to the number of procedures they perform.

Despite numerous attempts by clinicians and researchers, there is at present no well-established laboratory test that can detect or confirm the diagnosis of CFS. However, this search for a biologically based "litmus paper" test of CFS, has been questioned by some authors (e.g. Armon & Kurland, 1991) who suggest that this represents an implicit bias against psychological or social disability in favour of more acceptable physical (organic) disability. Nevertheless, this criticism may not be entirely fair given that the importance of assessing the role of psychosocial factors in CFS presentation is emphasised in much of the CFS literature.

A more central problem in the diagnosis of CFS lies in the adequacy of the CDC case definition. There are a number of potential pitfalls in making a diagnosis of CFS. Firstly, a diagnostic error could be made in failing to identify an underlying medical condition that could account for the presenting symptoms. A second point is made by Armon and Kurland (1991); they state that the precipitants of CFS may take the form of subtle or prolonged psychological exertion which are not considered in the case definition, and which can be easily overlooked by the diagnostician. Thirdly, the CDC criterion of a 50% reduction in daily activity level excludes those individuals who are forced by circumstance (e.g. socioeconomic status) to continue with their daily responsibilities (ibid). A further criticism directed against the CDC criteria is the lack of attention given to the concurrent psychological symptoms which, according to Abbey and Garfinkel (1991), are the most important aspects of the syndrome. A final but important point concerns the reliability of the account of the symptoms given by the patient to the doctor making the diagnosis. In this respect, it may be important to obtain collateral information in some cases.

1.2.2 Symptoms and Signs

The onset of CFS is typically preceded by a flu-like illness characterized by headache, upper respiratory tract infection, sore-throat, mild fever, a cough, myalgias and fatigue (Gordon, 1988). Onset may also by characterized by the appearance of myalgia and fatigue in conjunction with gastrointestinal symptoms (such as nausea, vomiting and diarrhoea). The more frequently experienced symptoms associated with CFS are summarized in Table 1-5. According to Komaroff (1993) there is considerable variation in the incidence and degree to which these symptoms are experienced; this inconsistency accounts for at least part of the diagnostic difficulty in assessing CFS patients. For example, one patient may be debilitated by constant nausea whereas another may be compromised by myalgia and parasthesias. Still others may experience severe depression as the main symptom. An examination of the data in Table 1-5 reveals that the most frequently experienced symptoms (in descending order) are: fatigue, low-grade fever, myalgias, sleep disorder, impaired cognition, depression, headaches and pharyngitis; these symptoms (with the exception of fatigue) may be experienced in up to 75% of cases.

The majority of patients are able to state the exact day on which their symptoms began, with some patients claiming that they contracted a flu-like infection that never seemed to go away (Komaroff & Buchwald, 1991; McCluskey & Riley, 1992). A history of the patient frequently reveals that their perception of ill-health is contrary to premorbid functioning, and many patients describe a premorbid personality that was energetic and high-achieving (Komaroff, 1993). Roughly one half of the patients studied by Komaroff and Buchwald (1991) reported that they had been under severe stress at the time they developed CFS although Boegman (1995) suggests that this figure may be closer to 85%. Examples of stressful events include: a new job, relationship problems, family illness or death, and moving house (ibid). The apparent lack of previously experienced somatic symptoms was investigated by Komaroff and Buchwald (1991). They compared the premorbid and post-illness frequency of some commonly reported symptoms in a group of 510 patients diagnosed with CFS. Results of their enquiries revealed the following comparisons (before vs. afterwards): arthralgias (6% vs. 76%); morning stiffness (3% vs. 62%); distractibility (4% vs. 82%); forgetfulness (2% vs. 71%); dizziness (4% vs. 61%); parasthesias (2% vs 52%;) sleep disorder (7% vs. 90%); irritability (4% vs. 68%); and cough (0% vs. 30%).

Table 1-5. Range and Frequency of Reported Symptoms in Patients with CFS

Symptom	Frequency (%)
Fatigue	100
Impaired cognition	50-85
Depression	50-85
Pharyngitis	50-75
Anxiety	50-70
Post-exertional malaise	50-60
Premenstrual worsening	50-60
Muscle stiffness	50-60
Visual blurring	50-60
Nausea	50-60
Muscle weakness	40-70
Arthralgias	40-50
Tachycardia	40-50
Headaches	35-85
Dizziness	30-50
Parasthesias	30-50
Dry eyes	30-40
Dry mouth	30-40
Diarrhoea	30-40
Anorexia	30-40
Cough	30-40
Finger swelling	30-40
Night sweats	30-40
Painful lymph nodes	30-40
Rash	30-40
Low-grade fever	20-95
Myalgias	20-95
Sleep disorder	15-90

(reproduced from Komaroff, 1993, p. 45).

Debilitating fatigue is of course the central feature of CFS although David et al. (1988) emphasize that some exploration of what this means to the patient and how it is manifested must be pursued by the diagnostician. This view is also shared by Kennedy (1988) and Sharpe et al.

(1991). Fatigue is a subjective sensation, and probably exists on a continuum with tiredness or weariness on one end and complete exhaustion at the other. Sharpe et al. (1991) distinguish two types of fatigue: (1) *physical fatigue* (experienced as a lack of energy or strength, and often located in the muscles); and (2) *mental fatigue* (characterized by lack of motivation and lack of alertness). They recommend that "in order to be regarded as a symptom fatigue must: (a) be complained of; (b) significantly affect the person's functioning; (c) be disproportionate to exertion; (d) should represent a clear change from a previous state; and (e) be persistent, or if intermittent, should be present more than 50% of the time" (Sharpe et al., 1991, p. 120).

The measurement of fatigue has remained a difficult area for researchers. Several attempts have been made to develop scales that measure both perception and severity of fatigue although according to Chalder et al. (1993), these have not been readily accepted in practice. Nevertheless, it is generally accepted that physical fatigue and mental fatigue should be evaluated separately in CFS patients (ibid).

Komaroff (1993) reports that 80% of patients with CFS have an exceptional post-exertional malaise. Despite the finding that exercise may be well-tolerated in these patients, it is followed 6-24 hours later by muscle pain and weakness. In addition, exacerbation of fatigue, cognitive dysfunction, adenopathy, pharyngitis and fever may be observed in 30-70% of post-exertional cases (ibid). This finding appears to be unique to CFS since it is not usually found in normal individuals, individuals with depression, or in the organic diseases that share some symptoms with CFS (Komaroff & Buchwald, 1991).

Another commonly reported symptom of CFS is impaired cognition, and this is found in around 50-85% of cases (see Table 1-5). It has been noted in the previous section of this chapter that concentration and memory difficulties are common and are included as criteria in some of the diagnostic systems. Patients also describe impaired verbal expression and periods of confusion. One of the psychometric instruments that has been able to discriminate between CFS patients and controls on the basis of perceived cognitive dysfunction, is the Cognitive Failures Questionnaire (Broadbent, Cooper, FitzGerald, & Parkes, 1982). Research by Smith (1991, 1992) has shown a significant difference between CFS patients and controls on questions such as: *do you read*

something and find you haven't been thinking about it and must read it again?; and, *do you forget why you went from one part of the house to the other?* (Broadbent et al., 1982).

It may be noted from Table 1-5 that the majority of patients with CFS also suffer from depression. The exact relationship between CFS and depression has been extensively debated in the literature and is more fully reviewed in Chapter 2. One point that can be made here is that the argument centres around whether depression is the result, cause, or co-variant of CFS. At the present time support is indicated for seeing depression as a result of CFS; Komaroff and Buchwald (1991) hold that whereas two-thirds of patients experience depression subsequent to getting CFS, less than 10% report that CFS followed a history of depressive illness. Furthermore although CFS and depression share common symptomatologies (e.g. fatigue, sleep disorder, myalgia, headache, and impaired cognition), the somatic symptoms associated with CFS seem harder to reconcile with depression by comparison. On the other hand, more recent approaches to the study of psychopathology have emphasized a dimensional approach (Oldham, 1991). Within this approach, attempts are made to correlate biological markers with a range of psychopathology (including affective disorders). Rather than seeing depression and CFS as mutually exclusive events, the dimensional approach would attempt to transcend categorical diagnoses in favour of identifying symptom clusters which could be characterized by both biological and psychological factors.

Although routine physical examination of CFS patients is usually unremarkable (Komaroff, 1993), a number of unusual and abnormal features are found in approximately 10-50% of CFS patients (see Table 1-6).

Table 1-6. Physical Examination Findings in CFS Patients

Finding	Frequency
Inflamed pharynx	40-60%
Posterior cervical adenopathy	20-40%
Abnormal Romberg (balance) test	10-20%
Impaired tandem gait (balance)	15-25%
Macular rash	10-20%
Pyrexia (fever)	10-20%
Low body temperature	20-30%
Hepatomegaly	5-20%
Splenomegaly	5-20%
Axillary adenopathy	5-15%

(reproduced from Komaroff & Buchwald, 1991, p.10)

The most common signs are swollen glands and pharyngitis. Komaroff and Buchwald (1991) also remark on the recurrent or persistent nature of the physical signs in some patients. Interestingly, a history of allergic illness is reported in some 50-80% of CFS patients and this contrasts with a prevalence of only about 10% in the normal population. Matsumoto and Ninomiya (1993) found an allergy prevalence of 78% in their Japanese CFS sample. These allergies (mainly cutaneous) improved spontaneously after onset of CFS, although it is noted that these investigators could detect no correlation between allergy and indices of immune system functioning. The significance of this finding is discussed later in the context of immune system functioning in CFS; it may however be stated here that there is some speculation that long-standing allergic illness may be a predisposing factor in the development of CFS (Komaroff, 1993). The finding of food intolerance in some CFS patients has also been the subject of investigation. In one study by Manu, Mathews, and Lane (1993), intolerance to foods was reported by 13.5% of a group of 200 consecutive CFS patients. A significant association with somatization tendency was demonstrated in those with multiple food intolerance; the authors concluded that a psychological rather than physical basis was responsible for the intolerance.

In comparison to the other symptoms associated with CFS, neurological signs such as ataxia, defective visual accommodation, focal weakness and unilateral parasthesias, appear to be

less common; when present they tend to be transient single events for most patients (Komaroff & Buchwald, 1991).

1.2.3 Laboratory Findings in CFS

It should be noted that while the case definition (diagnosis) of CFS is based primarily on the presence of the symptoms and signs outlined above, laboratory tests also assist in the diagnostic process if only at an exclusionary level (i.e. by eliminating common differential diagnostic entities). Medical laboratory tests are the investigative and confirmatory tools of the medical profession. Their purpose is to provide objective and replicable evidence of various biological markers which may have diagnostic value. A review of the literature reveals this area to be highly complex and not readily accessible to the psychologist or neuroscientist who lacks a medical background. Sophisticated medical knowledge is a prerequisite for the informed understanding and interpretation of such tests and as a result, largely falls out of the scope of this thesis. As a compromise, an attempt is made here to at least mention some of the procedures and the significance of test findings as they relate to CFS. It should be stated at the outset that the potential power of laboratory testing in CFS is to some extent diluted by methodological difficulties. According to Buchwald and Komaroff (1991), three common problems limit the strengths of conclusions that may be drawn: (1) there is often selectivity in the application of tests (i.e. they are not routinely applied in every case, while Calabrese, Danao, Camara and Wilke (1992) suggest that the precise choice of tests has not been standardized); (2) tests are often conducted at various points in the clinical course making comparisons across studies difficult (this is especially problematic in a condition in which symptoms may fluctuate over time); and (3) results of tests are usually reported with reference to the normal ranges, with few studies employing control groups. A fourth problem is highlighted by Straus (1993) when he indicates that there is little correlation between laboratory test results and clinical course (i.e. improvement or deterioration in the patient's symptomatology over time).

Shepard (1989), Komaroff (1993) and Fukuda et al. (1994) provide a summary of the recommended tests and common findings for CFS patients (see Table 1-7). Bell (1994) notes that the principal use of such tests should be to rule out other illnesses causing fatigue rather than being used to establish a CFS diagnosis. With regard to the last item in the table, Kyle and deShazo (1992) recommend that additional tests include an HIV antibody test, measurements of serial weight gain/loss and body temperature, as well as skin testing for allergies.

Table 1-7. Recommended Laboratory Tests and Representative Findings in CFS

Red cell count - normal.
ESR (erythrocyte sedimentation rate) and haemoglobin - normal.
WBC (white blood cell count) - may show a few atypical lymphocytes; a few patients may have persistently low or high cell counts.
Enzymes - LDH may be slightly raised, although creatine kinase within normal limits for most patients.
Immunoglobulins - variable: decrease in IgA and increase in IgM found in some patients.
Virology - Coxsackie IgM antibodies present in 10-20%; VP1 positive in about 60% of cases.
Urinalysis
Additional tests as clinically indicated to exclude differential diagnoses

(Fukuda et al., 1994; Komaroff, 1993; Shepard, 1989).

The tests appearing in Table 1-7 include measures of the blood constituents (red and white cell counts, ESR), serum chemistry (enzyme levels), and immunologic (immunoglobulins) indices. More detailed findings within these categories are reviewed below.

(1) *Hematologic Tests*

Standard blood tests generally fail to show specific abnormalities in the number of red and white blood cells of CFS patients. However, the shape of the cells may be altered in some cases. For example, unusual-appearing white blood cells (atypical lymphocytosis) are found in approximately 50% of cases (Komaroff, 1993). Research by Simpson, Murdoch, and Herbison (1993) also shows alterations in the shape of red blood cells, with CFS patients manifesting a greater percentage of flat as opposed to normal discoid-shaped cells when compared to healthy controls. Although the exact mechanism by which cell shape is changed is poorly understood, Simpson and colleagues

believe that abnormally shaped red blood cells result in impaired capillary flow and hence oxygen delivery to parts of the body where there are fine capillary networks (such as the muscle and brain). This in turn gives rise to behavioural manifestations of chronic tiredness and fatigue. Although Simpson's work has not achieved widespread acceptance by the medical profession (personal communication, August 1994), it is interesting from the point of view that it implicates reduced blood flow to the hypothalamus. Hypothalamic disturbance has been implicated in approximately 50-60% of CFS patients (Bakheit, Behan, Dinan, Gray, & O'Keane, 1992; Behan, Behan, Gow, Cavanah, & Gillespie, 1993).

(2) *Serum Chemistry Tests*

Approximately 20% of CFS patients are reported to have modestly elevated levels of transaminases (Buchwald & Komaroff, 1991). These are enzymes which appear in the liver, heart and other tissues; they play a role in normal cell metabolism and an elevated level implies a degree of liver dysfunction. Fatigue is a common manifestation of liver dysfunction.

(3) *Immunologic Tests*

The link between CFS and a dysfunctional immune system has received much attention from researchers attempting to establish causality in the CFS syndrome. As a result, most studies have paid at least some attention to immunologic findings. The abnormalities reported have included evidence of immune activation as well as immune suppression. Current opinion according to Levy (1994), is that the profile of immune system abnormalities (typically a hyperactive response involving CD8+ cell activation) resembles the immune system response to acute viral disease. Nevertheless, it seems important not to conceptualise immune system dysfunction in absolute terms. In this regard, Gorensek (1991) describes the immune abnormalities as evidence of "mild dysregulation" rather than being indicative of immune deficiency (as might be seen in AIDS).

It would be fair to say that despite initial enthusiasm for the application of laboratory tests as diagnostic tools, prevailing opinion is that they are of limited use in the diagnosis and treatment of CFS. Fukuda et al. (1994) comment that in their experience, persons with chronic fatigue often receive either inadequate or excessive medical evaluations and that inappropriate tests are often employed to diagnose the condition; a practice they feel should be discouraged. A similar

viewpoint is held by Komaroff (1993) who is of the opinion that until specialized laboratory tests attain proven diagnostic efficacy, none should be used routinely in patients with suspected CFS. It seems reasonable to expect that further research in this area will be conducted in an attempt to find biological markers of CFS. At the same time however, it is important to acknowledge the view held by Wessely (1991b) that the pursuit of a biological basis does not serve the patients' best interests if it is done with the purpose of finding objective evidence to support the clinical picture (i.e. it ignores the validity of the psychosocial disability).

1.2.4 Epidemiology

> Epidemiology, as a science, classically attempts to determine not only how many people in a given population currently have a specific illness (prevalence) and whether the illness in question is increasing or decreasing (incidence), but also what factors are associated with the development of the illness (Gunn, 1994, p. 10).

Given the difficulties inherent in the diagnosis of CFS, it is hardly surprising that little is known about its epidemiology. This is an unfortunate gap in the CFS literature, since epidemiological research could be potentially useful in forming a conceptual model of CFS etiology and transmission. Grufferman (1991) outlines what he considers to be some of the more important priorities in conducting epidemiological research into CFS: (1) the diagnostic criteria for CFS need to be refined to allow for more precise inter-study comparisons; (2) although it is known that CFS occurs in both endemic (sporadic) and epidemic form, further information on the natural history and outcome of the syndrome is needed; and (3) reliable statistics on the incidence, prevalence and possible mortality are still lacking.

Prevalence figures for CFS range from 3 to 1400 cases per 100,000 in the earlier studies (Behan et al., 1985; Spracklen, 1988). This range possibly reflects the diagnostic uncertainty that predated the 1988 CDC criteria. An estimate of 150,000 sufferers in the UK alone is reported by Spracklen (1988), while an Australian prevalence rate of 1 case per 3,000 persons is reported by

Lloyd, Hickie, Boughton, Spencer, and Wakefield (1990). Prevalence rates subsequent to the publication of the CDC criteria seem markedly less; Gunn, Connell, and Randall (1993) report a range of 2.3 to 7.4 per 100,000 of the general populations in a recent CDC surveillance study of four geographically distinct metropolitan areas. However, there are indications that this represents a minimum conservative prevalence estimate based on a limited sample of referred patients; in fact, prorated estimates of non-referred cases increased to 8.6-16.8 per 100,000 (ibid). A further problem with this study was the conservative application of the diagnostic criteria (45% of the referred fatigued patients failed to meet the CDC criteria on the grounds of a pre-existing psychiatric disorder; this included a reactive depression following the loss of a child some 10 years previously in one of the patients). Recently, the prevalence of CFS in the Netherlands was investigated by Bazelman et al. (1996). Compared to the CDC surveillance study figures mentioned above, an appreciably higher prevalence of CFS was reported (127 cases per 100,000).

The current prevalence of CFS in South Africa is unknown although a specialized CFS unit was established at Groote Schuur Hospital (Cape Town) in 1993. A recent pilot study revealed that during the first year of operation 87 patients were referred, but only 45 (51%) satisfied CDC diagnostic criteria (Katz & McDonald, 1996). The majority of patients diagnosed were female (88.9%) and the predominant group was comprised of white, married individuals aged 35 to 44 years. Additional demographic findings of this and other studies are commented on below:

(1) *Sex*

Females are particularly at risk for CFS, with prevalence rates being approximately eight times those of males (9.6 to 25.7/100,000 vs.1.4 to 3.2/100,000); in short, over 80% of CFS patients are women (Gunn et al., 1993). It is difficult to know what conclusions to draw from this finding given that most of the patients (55-60%) who consult a primary care practitioner are women (Komaroff & Buchwald, 1991). One possibility which presupposes a viral cause or trigger for CFS according to Spracklen (1988), is the fact that women are susceptible to moniliasis (a type of vaginal infection). Nevertheless, the exact relationship between moniliasis, susceptibility to infection and CFS is not well-established. On the other hand, Manu et al. (1993) interpret the over-representation of women as evidence against an infectious etiology for CFS. Vallings (1996)

suggests that the female preponderance of CFS sufferers may be due to hormonal factors, particularly estrogen shortage; again, this hypothesis has not been adequately investigated.

(2) *Ethnic background*

CFS appears to be affect mainly whites (7.6/100,000 compared to less than 1 per 100,000 non-whites) according to Gunn et al. (1993). This may be a spurious finding determined by socioeconomic variables and access to, or usage of, health care facilities. However, even in communities of black majority, CFS patients are generally white according to Manu et al. (1993). In a recent South African study, Katz and McDonald (1996) suggest that the absence of African referrals to a Cape Town hospital outpatient CFS unit might reflect the cultural acceptance of fatigue as a valid (i.e. non-pathological) somatic symptom.

(3) *Age*

The average age of patients in the CFS literature is 37.6 years, with the average age of onset being 30.2 years (Komaroff & Buchwald, 1991). Spracklen (1988) suggetss that the age group most at risk lies between 20 and 40 years, while Bazelman et al. (1996) found that 55% of their sample was aged between 24 and 44 years ($N = 112$). Komaroff and Buchwald (1991) report a wide age incidence range of 11-60 years, although more recent studies have given some attention to paediatric cases of CFS in which the age range extends down to five years of age (Bell, 1994; Bell, Bell, & Cheney, 1994; Walford, Nelson, & McCluskey, 1993). One of the prospective participants in the current study was 72 years of age, suggesting that exceptions to the published literature do occur.

(4) *Socioeconomic variables*

The term "yuppie flu" which was popularised in the media in the late 1980's, suggests that CFS is an illness which primarily affects well-educated and high earning/achieving individuals. On the other hand, it could be argued that this is an artifact related to earning potential and subsequent ease of access to medical specialists. In any event, the term "yuppie flu"is a misnomer given that CFS affects individuals from all socioeconomic groups (Levine, 1994; Wallace, 1991). Nevertheless, the health care and teaching professions appear to be particularly at risk (Jason et al., 1994; Levine, 1994; Spracklen, 1988). An recent view on the association between CFS and

a stressful, fast-paced lifestyle is mentioned by Ware (1993). He suggests that individuals who develop CFS may have a tendency to oversubscribe to social norms that endorse exhaustion as a way of life.

(5) *Geographical variables*

CFS has been reported from widely dispersed geographical regions around the world including the UK, Australia and New Zealand, Israel, North America, Asia, Africa and Europe (Klonoff, 1992; Shafran, 1992). In 1988 it was estimated that there may be as many as 5,000 sufferers in South Africa (Spracklen, 1988), although Katz and MacDonald (1996) suggest that CFS was over-diagnosed by practitioners who referred fatigued patients to the specialist unit at Groote Schuur Hospital. One point of interest is that CFS appears to be over-represented in the first world industrialized nations; nevertheless, researchers who have attempted to explain this phenomenon suggest that cross-cultural parallels exist in non-Western societies. Ware (1993) reports that fatigue-related disorders are seen in both East Asia and India (where it is referred to as *kamzori).*

Perhaps one of the most serious criticisms that can be directed at the epidemiological research on CFS (aside from the diagnostic difficulties already mentioned) is that current knowledge is based on a limited number of studies that have seen referred patients. There are some indications in the literature that many patients with a potential CFS diagnosis may have rejected further input from the medical profession and are seeking treatment from alternative health-care practitioners. Grufferman (1991) maintains that in order to overcome this selection bias, greater attention needs to be paid to securing prospective research participants that represent all cases in the community from which they are drawn. He indicates that this could be achieved through random selection of individuals in the community under study, with subsequent interviews and medical confirmation/collaboration of symptoms. While representing an ideal, such strategies are likely to be expensive and possibly impractical in some situations.

(6) *Additional risk factors - who gets CFS?*

One intriguing but perhaps unclear aspect of CFS, concerns those at risk for developing the syndrome; in this respect Klonoff (1992) is of the opinion that inadequate information exists on the predisposing risk factors. As mentioned above, the view that CFS is restricted to a particular

socioeconomic group has largely been discredited on the basis of research which has investigated risk factors. Nevertheless, there is some evidence indicating premorbid distress precipitated by negative life events such as overwork, exhausting or maladaptive lifestyles, and personal or relationship difficulties in a high number of individuals who develop CFS. The Type A behaviour pattern has been specifically mentioned as a risk factor which may serve to increase vulnerability to CFS (Lewis, Cooper, and Bennett, 1994). Extracts from representative cases are cited below:

> [Female Patient] - I was an extremely energetic sort of person. Physically I was in very good shape. I was working 12-13 hours a day, including weekends, going to school nights, and teaching. I had a husband, children, kept up with the laundry, cooked on weekends for the week. Until recently, I hadn't had a vacation in years.
>
> [Male Patient] - I was working probably 60 hours a week and some weeks a lot more. There wasn't enough time to get everything done. And things that needed to get done were assigned to me because my boss knew I would get them done. So he really loaded me down with a lot of stuff. And I should have said "no", but I didn't, because, you know, I thought, "I'm superman. I'm the guy who can get it all done. Nobody else can do it; they're all such a lazy bunch of idiots. I'll take care of it. I'll show them all". In retrospect, I mean, it was really pretty dumb.
>
> (Ware, 1993, p. 64).

Obviously, not everyone who works excessively or who is stressed develops CFS (i.e. overwork or stress *per se* cannot provide a complete etiological explanation). Rather, the pathogenesis would seem to involve multiple factors which may or may not include stress and/or various psychological conditions (such as depression). Some of the environmental factors (excluding direct bacterial, viral or fungal infection) which have a possible causal link with CFS include ingestion of raw milk, presence of a second family member with CFS, a history of allergies and asthma, and a high pre-illness ingestion of non-prescription health supplements (Bell et al., 1991; Khan et al., 1993). In the study conducted by Bell et al., a wide range of additional risk factors were found to be non-significant. These included ingestion of various food types (e.g. eggs, shellfish, cheese), type of home heating, experience of outdoor camping, proximity to orchards or farm land, and exposure to animals (pets and domestic animals).

1.2.5 Pediatric and Adolescent CFS

As mentioned in the previous section, children and adolescents are also vulnerable to CFS, although it seems that in comparison to adult groups, the illness is considered to be both less debilitating and shorter lived (Vereker, 1992). However, the symptoms are similar (with the exception of less prominent neurological symptoms) and include lethargy and fatigability. Prominent symptoms in children according to Marcovitch (1991) and Bell (1994) include headache, dizziness and light-headedness, back and limb pains, abdominal pain and nausea. Bell et al. (1994) studied 27 children with CFS and found that 74% experienced an acute onset of symptoms which lasted for an average of 34 months (mean age of onset was 12.22 years).

Virtually all studies on pediatric CFS highlight the diagnostic difficulties encountered in this particular patient group, although in comparison to children, the diagnosis appears to be more easily made in adolescents, possibly due to their superior (i.e. more mature) symptom reporting ability. Bell (1994) suggests greater day-to-day symptom variability in children; one day they might complain that sore throat and headaches are the worst symptoms, followed by abdominal pain the next day and so on. Furthermore, he suggests that in comparison to the more acute onset in older children and adolescents, CFS onset in children aged 5 to 10 is gradual. This gradual onset may be difficult to identify and operationalize in meaningful terms; however, everyday examples are mentioned by Marcovitch (1991) who comments that children who have premorbidly been able to ride a bicycle without rest for several kilometres, may suddenly find that they are unable to pedal for more than a few hundred metres before requiring rest. A more serious case study is presented by Sidebotham, Skeldon, Chambers, Clements, and Culling (1994):

> A previously healthy 12 year-old girl presented with a three month history of general debility and weakness together with some depressive symptoms following an episode of flu. In addition to her tiredness and lethargy, she had a poor appetite and complained of headaches and generalized muscle aches. She gradually deteriorated over the following months, becoming weaker, particularly in her lower limbs; she progressed to using crutches and then a wheelchair, finally becoming bed-bound for most of the time. She found concentration difficult and soon

> stopped attending school. Home tuition was arranged for a short period each day. A year into her illness she was almost totally dependent on her parents, was requiring nutritional supplements to maintain adequate calorific intake, had become extremely sensitive to any sensory stimuli, and took to wearing dark glasses and gloves at all times. Prolonged immobility has led to the formation of a bladder stone and an equinous deformity of the foot. The family were reluctant to involve the child psychiatrist in her care (p. 111).

Pediatric CFS experts (e.g. Marcovitch, 1991; Sidebotham, 1994; Strickland, 1991; Sturtz, 1991; Vereker, 1992) have highlighted the diagnostic difficulties in cases such as these, since viral infections can interact in a complex way with both developmental (e.g. dependence vs. independence) and psychological factors (e.g. childhood depression and somatizing behaviour in distressed children). For example, Vereker notes dissociative symptoms and hysteria in a 16 year-old adolescent with a history of glandular fever at age 11 when she suddenly developed paralysis of the lower limbs with selective amnesia; follow-up on this particular case revealed a complete remission of the paralysis three days after admission to a specialised hospital unit. In another case, the mother of a 13 year-old girl noticed that her daughter's fatigue and misery were substantially reduced during periods spent away from home. Psychological comorbidity is highlighted in a study by Wilson, Kusumakar, McCartney, and Bell (1989) in which unexplained crying and a fear of dying were found in a group of children aged 5-12 years ($N = 45$).

Problems of differential diagnosis are highlighted by Vereker (1992) when she suggests that childhood emotional disorders are less well differentiated than adult disorders and therefore more difficult to identify. In addition, various psychosocial factors have been used to explain the prolonged and severely debilitating symptoms that some CFS children and adolescents experience. Sidebotham et al. (1994) hold the view that "the secondary effects of long-term illness, disability and absence from normal life experiences compound the adolescent's problems and a stage can be reached where the prospect of rehabilitation and a return to health presents almost overwhelming anxiety" (p. 111). Other maintaining factors mentioned in the literature include poor social adjustment, problems at school, and premorbid high expectations of achievement (Vereker, 1992). Recommended remedial actions include an active rehabilitation program coupled with psychiatric intervention where indicated (ibid).

1.2.6 Course and Outcome

A series of studies by Komaroff and Buchwald (1991) and Komaroff (1993) on more than 300 CFS patients have revealed that the typical CFS patient has been ill for an average of nearly 6 years (range 0.5-22 years). Approximately 25% of these patients describe themselves as house-bound and unable to work, and a further third claim that they can only work part time. Typically, the course of the symptoms waxes and wanes with patients reporting "good" and "bad" days. Remissions of fatigue may last for a few days, weeks or even months with some patients relapsing periodically while others seem to recover more or less completely. According to the clinical observations and experience of Bell (1994), there are several factors which directly influence the speed and degree of recovery; these include the following:

(1) *nature of onset* (e.g. acute versus gradual) - acute onset such as might follow a flu-like illness generally results in a slow, steady, and more or less complete recovery over several years. This contrasts with a gradual onset which is often less severe in terms of symptomatology but from which the recovery is less complete (see Figure 1-1);

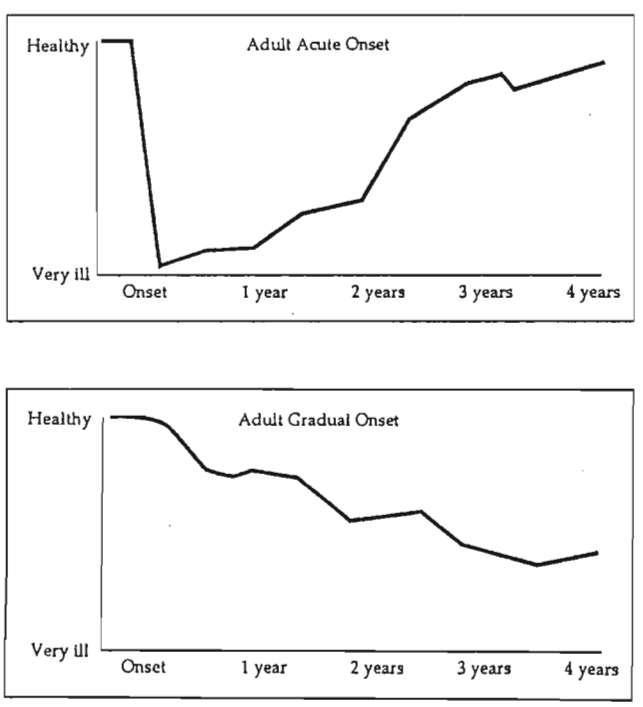

Figure 1-1. Clinical Course of CFS: Acute versus Gradual Onset (Bell, 1994, pp.139-140).

(2) *age at time of onset* - in contrast to adolescent and adult onset in which symptoms resolve reasonably quickly, childhood onset generally results in slow and incomplete recovery;

(3) *pattern of relapses* - severe and extended relapses are a negative prognostic sign;

(4) *prominence of neurologic symptoms* - patients who have persistent and severe neurological symptoms are likely to have a poorer outcome.

More rigorous outcome studies are somewhat sparse in the literature; this is probably due to the relative recency of the syndrome and the time constraints that govern longitudinal studies. Much of the outcome literature is based on anecdotal personal experience (e.g Behan & Bakheit, 1991; Bell, 1994). Naturally, the minimum length of the illness is six months (as determined by the diagnostic criteria). The clinical impression of Behan and Bakheit is that those individuals who have experienced the illness for more than a year without complete or partial remission of symptoms have a poor prognosis. They further maintain that the majority of patients with CFS experience a gradual recovery with partial remission and that outcome is more favourable when there is an avoidance of situations that exacerbate the symptoms. Remission of symptoms during pregnancy is also reported by these authors; this finding appears to indicate a hormonal interaction with symptomatology. Bell (1994) states somewhat pessimistically, that few patients will return to premorbid health and that persistence beyond five years is a poor prognostic sign.

Spracklen (1988) reports that if the diagnosis is made within three months of the onset of illness then more than 50% of patients recover within one year. The more common course however is for the symptoms to last anything between two and five years. In rare cases it may continue for 10 or 20 years. In contrast to the view of Bell (1994), Sidebotham et al. (1994) suggest that children tend to show more rapid improvement than adults. Psychiatric complications have been documented in the literature; Kendell (1967) describes two case studies of markedly negative outcome (one patient developed a psychosis while the other developed *grand mal* epilepsy). There has been at least one documented suicide of an American woman who was overcome by the burden of her symptoms (Bell, 1994).

One outcome study followed 102 adults for approximately a year and found that only 28% showed improvement (Shafran 1991). In a prospective follow-up study, Gold et al. (1990) studied 26 adults with fatigue lasting longer than nine months; 13(54%) were unable to engage in full-time work at the end of three months. Twelve patients were followed up over the course of a year. Of these, eight (67%) had continuing fatigue but only two (17%) were unable to work full-time. Unfortunately, the small sample size and somewhat limited outcome criterion makes it difficult to form any meaningful conclusions.

Sharpe et al. (1992) conducted a follow-up study of 144 CFS patients over a four-year period using postal questionnaires. Of the 81% of patients who responded, it was found that a third remained impaired at two to four years from CFS onset compared with 73% who were impaired at six months. Impaired functioning (as reflected in reduction of lifestyle activities) was significantly associated with a number of patient factors, including belief that their illness had a viral cause, alcohol avoidance, limiting exercise, changing or leaving employment and belonging to a self-help organization and emotional disorder. Unfortunately, the findings did not indicate the direction of causality underlying the associations; this limits the study conclusions about factors that perpetuate the illness. For example, emotional distress could be both a cause and consequence of functional impairment. Wilson et al. (1994) conducted a three-year follow-up on 103 of their patients. Although all patients showed some improvement over time, only 6% of cases were fully recovered after three years. Most patients continued to experience some degree of disability in one or more spheres of their life (e.g. 40% found social activity impossible, whereas 20% were unable to engage in physically strenuous activities). As with the Sharpe et al. (1992) study, belief of an underlying physical disease was a poor outcome predictor in this group of Australian patients. However, Wilson's study has been criticised by Blatch and Blatt (1994) for the use of subjective self-rated outcome measures and dubious statistical analysis.

Possibly the best outcome study comes from Bonner et al. (1994). They conducted a four-year follow-up on 46 CFS patients who had previously been offered treatment by the authors. Twenty-nine of these patients were assessed on a range of questionnaires including the General Health Questionnaire (GHQ), the Hospital Anxiety and Depression Questionnaire (HAD) and the Beck Depression Inventory (BDI). Results showed that 10 (34%) of the patients continued to meet the criteria for CFS. Of the 22 patients who accepted treatment four years previously,

sustained improvement was noted in 14 patients (64%). A high incidence of psychiatric symptomatology (especially somatization and depression) characterized those who had not improved at follow-up. This latter finding of generally poor outcome in CFS patients with coexisting depression was supported in a recent study by Bombardier and Buchwald (1995). They conducted an 18-month follow-up study of 445 CFS patients and found that while 64% of this follow-up group reported improvement, only 2% reported complete resolution of symptoms.

A relatively new approach to the treatment of CFS has involved inpatient management. For example, the Havering Hospitals Trust in the UK claims that 69% of inpatients have an increased level of ability (dependent measures not specified) six months after discharge (*Therapy Weekly*, July 4, 1996, p.3).

To conclude this section, the few outcome studies that have been done generally show a positive outcome for the majority of individuals who are diagnosed as having CFS. In addition, it appears from the study by Bonner et al. (1994) that prognosis is maximized in individuals who are offered systematic intervention. In this regard, cognitive behaviour therapy is one approach that appears to hold some promise (Sharpe, 1991). This and other treatment options are reviewed in section 1.4. Of interest, is the common finding that poor outcome is associated with premorbid or concurrent psychiatric illness as well as conviction that the symptomatology has a physical basis (i.e. psychosocial denial). Such findings obviously have treatment implications, although to date, no studies have investigated differences between patients who attribute their symptoms to external sources and those who acknowledge a psychological component (Lawrie & Pelosi, 1994).

1.2.7 Differential Diagnosis

In terms of the CDC case definition, a number of well-established medical disorders giving rise to fatigue must be excluded before a diagnosis of CFS can be made. This is commonly done on the basis of a thorough history, physical examination and appropriate laboratory investigations (Sharpe et al., 1991). Conditions to be excluded are malignancy, autoimmune disease, infections,

chronic psychopathology, neuromuscular disease, endocrine disease, drug dependency or abuse, exposure to a toxic agent, and other known or defined chronic pulmonary, cardiac, gastrointestinal, hepatic, renal, or haematologic disease (Holmes et al., 1988). The more common representative conditions are summarized in Table 1-8 (Behan & Bakheit, 1991; Calabrese et al. 1992; Chester & Levine, 1994; Packer, Sauriol, & Brouwer, 1994; Shepard, 1989; Straus, 1991).

Table 1-8. Differential Diagnosis of CFS

CNS	Myasthenia gravis
	Multiple sclerosis
	Obstructive sleep syndromes and narcolepsy
	Postpolio syndrome (poliomyelitis)
Endocrine	Hypothyroidism
	Addison's Disease
	Diabetes
Infections	Lyme Disease
	Human immunodeficiency virus infection
	Brucellosis
	Tuberculosis
	Toxoplasmosis
	Salmonellosis
Psychiatric	Endogenous depression
	Histrionic personality disorder
	Generalized anxiety disorder
	Schizophrenia
Rheumatic	Fibromyalgia
	Systemic lupus erythematosus
Other	Chronic illness (renal, hepatic, cardiac)
	Drug side effects (e.g. beta blockers)
	Alcohol or other substance abuse
	Heavy-metal toxicity
	Pesticide exposure
	Lifestyle issues (inadequate exercise/rest)
	Total allergy syndrome
	Sick building syndrome

This list seems extensive, and complaints that the CDC exclusionary recommendations are virtually impossible to operationalize in practice, have been made in some medical quarters (Behan & Bakheit, 1991). These authors argue for example, that night sweats is a common symptom in the early stages of acquired immune deficiency syndrome (AIDS) and may predate other symptoms by several months. They also suggest that many of the conditions in Table 1-8 can be associated with myalgia, making differential diagnosis a difficult task. A further consideration is that chronic psychopathology is offered as a differential, yet this would exclude the possibility of conceptualizing CFS on a continuum that combines both biological and psychological factors.

Debilitating fatigue is a symptom common to many of the diagnostic differentials and some discussion on conditions which might be confused with CFS follows:

(1) *Depression*

Although the symptoms of depression and CFS may overlap (e.g. fatigue, somatization), there are a number of important discriminating features according to Behan and Bakheit (1991) and Komaroff (1993). Objections against viewing CFS as a type of depression include the following: a family history is often evident in certain kinds of depression; CFS does not usually result in impairment of libido and sexual ability; depression does not start suddenly with a "flu-like illness" and does not include symptoms such as light hypersensitivity and swollen lymph glands. Neuroendocrine profile are also different for the two groups. Further discussion on the association between depression and CFS may be found in Chapter 2.

(2) *Multiple Sclerosis (MS)*

Although CFS and multiple sclerosis are easily differentiated when the latter presents in a full-blown form, the initial symptoms in subtle onset multiple sclerosis can include profound fatigue with myalgia, emotional lability and depression (Behan & Bakheit, 1991; Packer, Sauriol, & Brouwer, 1994). These latter authors report that fatigue is a prominent symptom in approximately 78% to 89% of MS patients. Multiple sclerosis is apparently a difficult disease to diagnose; one study found that the average time between symptom onset and diagnosis was 43 months (Komaroff, 1993). It is therefore possible that during this time a diagnosis of CFS might be considered for at least some of these patients. There has been increasing use of patients with

multiple sclerosis as controls in CFS studies (De Luca et al., 1993; De Luca et al., 1995; Krupp et al., 1994). The value of this comparison is that it gives researchers an opportunity to tease out the more subtle symptomatology that may differentiate the two groups.

(3) *Systemic Lupus Erythematosus* (SLE)

This is also a disease that shares considerable symptom overlap with CFS (especially debilitating fatigue). SLE is defined as "an inflammatory connective tissue disorder of unknown etiology occurring predominantly in young women, but also in children" (Berkow & Fletcher, 1992, p. 1317). Although definitive laboratory tests are available, the test results may be ambiguous in the more benign presentations (Komaroff, 1993).

(4) *Brucellosis*

Brucellosis is defined as "an infectious disease characterized by an acute febrile stage with few or no localizing signs and by a chronic stage with relapses of fever, weakness, sweats and vague aches and pains" (Berkow & Fletcher, 1992, p. 109). It is acquired through direct contact with secretions and excretions of infected animals or by ingesting the dairy products of cows, sheep or goats. Although recovery from acute infection is normally complete within two to three weeks, symptoms of chronic infection may continue for months or even years (Swartz, 1988). In a follow-up study of 24 brucellosis patients who had been diagnosed up to 10 years previously, Cluff (1991) found that only 16 individuals made a full recovery within two to three months of symptom onset. Although brucellosis was a popular diagnosis given to fatigued patients prior to 1960 the brucellosis hypothesis (as a cause of chronic fatigue) was eventually discredited on the basis of studies conducted between 1951 and 1959 (Straus, 1991). Like CFS, the clinical picture in chronic brucellosis is contaminated with psychological factors which may serve to extend the illness (Straus, 1991). For example Cluff (1991) found that a tendency towards depression was the main predictor of delayed convalescence in his study.

(5) *Ciguatera*

Chronic fatigue may be precipitated by ciguatera, a relatively rare form of fish poisoning originating in reef-dwelling dinoflagellates (Pearn, 1996). After entering the piscine food chain, infection may be readily spread to fish-eating humans, especially those resident on the Pacific, Atlantic and Indian Ocean tropical and subtropical littorals. According to Pearn, acute

intoxication is also characterized by headache, parasthesiae, myalgia and athralgia. Protracted recovery (persisting for months or even years) may be seen in a small number of individuals. In addition to fatigue, symptoms may include reduced exercise tolerance and non-specific aches and pains. One interesting point raised by Pearn is that further food-chain effects may extend to pigs and chicken who are fed pellets containing fish meal.

(6) *Fibromyalgia*

The term "fibrositis" was proposed as early as 1904 to describe diffuse aches and pains for which no organic pathology could be found (Shorter, 1993). Today this syndrome is known as fibromyalgia and is defined as "widespread pain involving both sides, above and below the waist, and pain on digital palpation in 11 of 18 tender-point sites" (Calabrese et al. 1992, p. 1208). Fibromyalgia is a common condition with an estimated prevalence of some three to six million cases in the United States (Kroenke, 1991). Like CFS, the majority of sufferers are women with an average age of about 40 years at the time of clinical presentation (Moldofsky, 1993). The symptom similarity between CFS and fibromyalgia is has led some authors to consider these disorders to be closely related if not identical (Kirmayer, Robbins, & Kapusta, 1988; Schluederberg et al., 1992). The major difference according to Kyle and deShazo (1992) is that specific musculoskeletal signs (such as tender points and pain) must be present to fulfil the diagnosis of fibromyalgia, whereas not all CFS patients have enough muscle pain to elicit tender points on examination (Bell, 1994). Other discriminating features include the assertion that painful lymph nodes and acute febrile illness (fever) are not seen in patients with fibromyalgia (Moldofsky, 1993). As far as commonalities in symptomatology are concerned, research shows that not only muscle pain but also fatigue, recurrent headaches, sleep disturbance and psychological factors (such as depression and anxiety) are present in both fibromyalgia and CFS. Table 1-9 contrasts the clinical findings of 20 patients with fibromyalgia, 19 with CFS in which myalgias were prominent, and 8 CFS patients without myalgias. As with some of the more recent investigations of CFS (including the current study), Kirmayer et al (1988) found a high somatization tendency in patients with fibromyalgia.

Table 1-9. Discriminating Features of Fibromyalgia and CFS

Symptom	Fibromyalgia	CFS
Sudden onset	+	+ + +
Painful lymph nodes	-	+ +
Fever	-	+ +
More than 15 tender points	+ +	+
Morning stiffness	+ + +	+ +
Sleep disturbance	+ + +	+ +
Pharyngitis	+	+ +
Headache	+ +	+ + +
Anxiety	+	+ +

(Calabrese et al. 1992, p. 1208)

Apart from the overlap in clinical presentation, specialised studies indicate that both conditions manifest physiologic muscle dysfunction; e.g. low muscle tension, reduced blood flow, and abnormal phosphate metabolism (Calabrese et al., 1992). In addition, decreased natural killer cell functional activity, increased CD4/CD8 lymphocytes ratio and decreased CD8 cells are common to both conditions (Kyle & deShazo, 1992). Some studies have suggested that CFS and fibromyalgia may coexist; one study found that of 27 CFS patients, 19 (70%) also manifested clinical features of fibromyalgia (Krupp, Mendelson, & Friedman, 1991).

(7) *Total Allergy Syndrome*

Wilson (1990) notes that many patients with allergic disease have identical symptoms to CFS patients, while Bell (1994) reports that many individuals who develop CFS are likely to have a history of allergies (atopy) and that allergies may develop for the first time following CFS onset. Marshall et al. (1997) report that allergy is the most common premorbid condition in CFS, with a prevalence of over 80%. However, it is not clear whether atopy is a causal or outcome variable; with regard to the latter possibility, Bell (1994) maintains that atopy could reflect an up-regulated immune response. The mechanism of allergy reaction is that affected individuals become hypersensitive to various substances that enter the body in foodstuffs or are inhaled or absorbed through the skin. Typically, there is an immunological response (e.g. rhinitis, sneezing, dermal rash) as the body interprets the allergen as if it were an invading virus or bacteria (Bell, 1994). Common allergies include pollens, moulds, house dust, and chemicals (dental fillings have even

been implicated). These sensitivities can usually be confirmed upon laboratory testing, and in some cases treated using a series of desensitization exposures. Clinical ecologists have coined the term "total allergy syndrome" or "20th century disease" to explain chronic and excessive responses to various allergens (Straus, 1991).

Stewart and Raskin (1985) performed a psychiatric assessment of 18 people referred to them with the total allergy syndrome. Clinical and laboratory findings were normal. Psychiatric symptomatology was present in 10 of these individuals who manifested varying degrees of psychosis, anxiety and depression. An additional seven exhibited somatoform disorders. Nevertheless, the legitimacy of whether total allergy syndrome provides an explanation for some of the symptoms associated with chronic fatigue syndrome remains equivocal. For instance, a study by Straus et al. in 1988 found that 50% of patients with CFS demonstrated allergies to inhalants or food (as cited in Straus, 1991). This contrasts with an incidence of only 15%-20% in the normal population. However the link between viral infection, CFS, and allergic reaction is not clear, and Wilson (1990) suggests that a complex interplay exists between a viral infection, subsequent potentiation of a pre-existing (albeit subclinical) allergic response, and the resulting immunological challenge. The consequences are the emergence of central nervous system symptoms and psychosomatic illness. Despite these findings, it seems unlikely that a chronic allergic response can successfully provide an explanation for the range of other symptoms associated with the disorder. Nevertheless, at least one recent study reports complete symptom resolution following nasal surgery in a patient previously diagnosed as having CFS (Chester, 1993).

Possibly related to total allergy syndrome, is a relatively new occupational disease known as sick building syndrome (SBS). According to Chester and Levine (1994), it is a condition characterized by upper respiratory complaints (e.g. rhinitis, conjunctivitis and cough), fatigue, and headache. Outbreaks are apparently common in employees who work in the air-conditioned closed environments of modern high-rise buildings, and it has been noted that symptoms often abate during weekends when employees are away from the office. The cause is currently unknown although affected individuals often complain of "stale air". This may have some substantiation given that inadequate ventilation has been mentioned as a probable cause in 53% of the buildings investigated by the American National Institute for Occupational Safety and Health (ibid). Using

a questionnaire survey method, Chester and Levine describe three outbreaks of SBS associated with the development of CFS and found that there appears to be considerable overlap in clinical presentation between the two conditions. The most common symptom reported by SBS individuals was fatigue, but neurologic symptoms of decreased concentration and memory were also reported at rates significantly greater than non-affected fellow workers. The authors called for the establishment of a working definition for SBS.

Pesticide exposure has also been investigated as a possible etiological agent in the development of CFS. Dunstan et al. (1996) recently studied the serum levels of chlorinated hydrocarbon pesticides in 39 CFS patients and 34 age- and sex-matched controls (17 of the CFS patients reported a history of toxic chemical exposure). Results indicated that the CFS group had a higher total organochlorine level than the control group (there were no differences in pesticide concentrations between those reporting and not reporting exposure). The authors called for further investigation of possible low level organochlorine bioaccumulation in CFS patients.

(8) *Chronic Candidiasis*

Many patients with chronic fatigue syndrome believe that a large part of their symptomatology can be explained on the basis of infestation from the yeast *Candida albicans*. Although *Candida albicans* forms part of the natural flora and fauna of the human gastrointestinal tract, many CFS patients complain of candida overgrowth. Numerous factors including repeated exposure to antibiotics, oral contraceptives, and inadequate diet are thought to promote the overgrowth of candida, resulting in the release of immunotoxins that compromise the immune system. At least two popular books and numerous anecdotal reports in the medical literature published in the 1980's describe the "yeast connection" (Renfro, Feder, Lane, Manu, & Mathews, 1989). A wealth of information about the Chronic Candidiasis Syndrome is also available on the Internet (Darren, 1996). Treatment is aimed at specific antifungal treatment in conjunction with dietary manipulation to reduce the amount of sugars and complex carbohydrates which promote the growth of candida.

The extent to which candida overgrowth contributes to an explanation of CFS symptoms is somewhat controversial, although Straus (1991) claims that this is largely due to a shortage of mycologic studies in CFS patients. One argument against the yeast connection is based on a

carefully constructed study by Renfro et al. (1989). One hundred consecutive CFS patients referred to a University-based health centre were interviewed and subjected to a complete physical examination (including extensive laboratory testing). Eight patients who attributed their ill-health to yeast overgrowth were then compared with others who did not express this belief. No differences were found between the two group on the basis of the physical findings and laboratory results (i.e. not a single patient manifested clinical evidence of active candida infection). However, a significantly higher incidence of underlying psychopathology was noted in the group of patients who believed they were infested with candida. This suggested that these patients were expressing psychological distress through somatic channels. Perhaps the largest study to examine the role of *Candida albicans* in CFS is that of Jessup, who presented a report on 1100 fatigued patients at the 1989 International Conference on CFS (as cited in Galland, 1991). Interestingly, almost all of the patients in his study reported alcohol or sugar addiction prior to symptom onset. Jessup initiated a five- month treatment regime of ketaconazole (an antifungal agent) together with a diet free of alcohol, added sugar and fruit. Recovery was seen in 84% of the sample, leading Jessup to conclude that the CFS symptoms arose from a systemic toxin produced by intestinal colonization of yeast. Others are sceptical of this simplistic cause and effect relationship; Galland (1991) makes the point that the improvement in Jessup's patients could have been due to the interaction of ketaconazole with the immune system rather than being due to any specific antifungal effect. Likewise, Bell (1994) believes that in affected individuals, candida is present because of the illness and is not the cause of it (i.e. he suggests that candida overgrowth occurs in the face of immunosupression). This viewpoint is not shared by Cater (1995) who, in a recent review of the literature on this topic, suggests that the relatively non-specific activation of the immune system in CFS could easily accommodate *Candida albicans* as an etiologic agent in a significant number of CFS patients. Cater cites evidence showing that the immune status of patients affected by chronic candidiasis and those with CFS show striking similarities, and concludes that the immunological depression from Candida infection may be the cause of CFS in some patients. It seems that further investigations are required in this area.

1.3 THE PATHOGENESIS OF CHRONIC FATIGUE SYNDROME

The cause of CFS is currently unknown although several etiological explanations have been proposed. There is agreement that for at least some cases, symptom onset is associated with a viral infection which acts as a trigger for subsequent immune system activation/dysfunction. Nevertheless, despite the acceptance that immunological dysfunction lies at the core of CFS, little is known about the complex interplay of psychological, immunological and neurological factors that are thought to give rise to the clinical presentation. This section of the literature review presents the proposed viral etiologies that have been implicated in CFS, and includes discussion on how these may be associated with immune dysfunction. The psychological and neurobiological dimensions are examined separately in Chapters 2 and 3.

1.3.1 Viral Infection

It was mentioned in the previous section that many individuals with CFS give a history of an infectious illness as the precipitating event; Boegman (1995) reports that approximately 72% of CFS patients provide evidence of a viral onset. Although this infection can be traced to parasitic or bacterial causes in a small number of individuals, the majority of cases are assumed to have been infected with some kind of virus (Shafran, 1991). A viral etiology for CFS was suggested as early as 1978 but it seems that virologists are still unclear of whether this might involve a single (as yet undiscovered) virus, or whether other agents are involved in the pathogenesis of the syndrome. The quest to uncover the exact pathogen is not strictly academic, since knowledge in this regard has treatment implications; i.e. approaches to the cure of CFS can be focussed on combatting the infectious agent and inoculating those who are at risk of infection.

The problem of viral inference in CFS is that it is difficult to establish causality between specific viral infection and development of CFS. Infections caused by a whole range of viruses occur throughout the community all the time; most give rise to either trivial conditions which may be flu-like, or in some cases an asymptomatic picture may result (Sutton, 1978). The difficulties inherent in defining the pathogenesis of CFS in causal terms are summarized by Evans (1991):

(1) A clinical syndrome can be produced by several different causative agents.

(2) A single causative agent often can produce several different syndromes.

(3) The cause, or the syndrome produced by it, may vary according to age group, cultural setting, geographic area, portal of infection, immune status, and genetic makeup of the host.

(4) Multiple causes or cofactors are usually required to produce clinical disease amongst those infected.

(5) The causes of many common clinical syndromes are incompletely identified.

(Evans, 1991, p. 58).

Historically, three main viral groups have been implicated: the enteroviruses (which includes Coxsackie A and B, polio and echoviruses);[2] the herpesviruses (which includes Epstein-Barr, cytomegalovirus and the human herpesvirus type 6); and more recently the retroviruses, such as human T-lymphotropic virus types I and II (HTLV-I and II), although additional viruses (such as Borna disease virus) have been implicated in some studies (e.g Ikuta et al., 1996). Representative viruses are summarized in Table 1-10.

Table 1-10. Viruses Implicated in CFS

Epstein-Barr Virus (EBV)
Cytomegalovirus (CMV)
Coxsackie A and B viruses
Human herpesvirus types 6 and 7 (HHV-6 and HHV-7)
Human T-lymphotropic virus types I and II (HTLV-I and HTLV-II)
Measles virus
Hepatitis A, B, and C viruses
Borna Disease virus

[2] According to Dowsett et al. (1990), there are 69 known enteroviruses; the favoured mode of transmission occurs via the faecal/oral route.

(1) *Enteroviruses*

The role of enteroviruses in CFS has received some attention, especially by UK researchers. An early study by Dowsett et al. (1990) retrospectively examined the medical records of 6,000 patients referred to their Scottish laboratory between 1975 and 1987; they found 420 cases of chronic relapsing fatigue. Of these, 205 cases were tested for the presence of Coxsackie B antibodies and 50% (103 cases) tested positive; an additional 124 patients were investigated for enteroviral IgM with 30% (38 cases) testing positive. In a more recent Scottish study, Gow et al. (1994) investigated 121 CFS patients for the presence of enteroviruses. In contrast to the methodology of seroprevalence used in other studies, they took muscle biopsies and compared them with samples collected from a group of 101 controls suffering from various neuromuscular disorders. Although 26.4% of the CFS patients and 19.8% of the controls tested positive for enteroviral presence, this failed to reach statistical significance.

(2) *Herpesviruses*

Infectious mononucleosis (i.e. glandular fever caused by the Epstein-Barr virus) has received the most attention as a potential culprit for CFS (especially from US investigators), although its implication in CFS has been the subject of much debate. Studies conducted in the early 1980's suggested that prolonged or recurrent episodes of EBV infection were associated with fatigue syndromes in some patients, and that this could be measured on the basis of levels of blood antibodies to EBV antigens.[3] However, the strength of this correlation and degree of causality has been questioned by subsequent researchers (Armon & Kurland, 1991; Dawson, 1987; Holmes et al., 1988; Straus, 1991). There appears to be increasing support for the contention that raised levels of EBV antibodies are present not because they are responsible for the illness, but because a dysfunctional immune system, allows for their reactivation (Bell, 1994). Furthermore, it has been noted that EBV antibodies may occur in conjunction with a range of different viral infections (including HIV and HHV-6) and are found in individuals suffering from stress and depression (Evans, 1991). This lack of specificity in causation suggests only that these various conditions

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Discovered in 1964, EBV belongs to the herpes virus family and it has been found that up to 95% of all adults have been infected by EBV at some point during their lives (Bell, 1994). Generally speaking, infection during childhood leads to a relatively benign flu-like illness; severe infection, or infection which occurs in adolescence or adulthood, earns the diagnosis of infectious mononucleosis. Like other herpes viruses, EBV remains in the body in a latent state unless reactivated by an immune deficiency (ibid).

may reactivate a previous EBV infection leading to a chronic condition (CEBV).

Even in CFS studies where positive EBV serology has been demonstrated, there appears to be little clinical (or psychiatric) difference between fatigued individuals, and others in which EBV serological testing is negative. For example, 200 chronically fatigued patients were examined for the presence of EBV antibodies in a study by Mathews, Manu and Lane (1991). Of these, 35 patients tested positive for chronic or reactivated EBV infection and this group was then compared to 35 age- and sex-matched fatigued controls. Physical examination and serological laboratory testing failed to find any group differences; the authors concluded that the value of EBV antibody testing in fatigued patients was limited. It was however noted that the EBV positive cases were more likely to meet CFS diagnostic criteria (14% versus 0%, $p < .03$).

Although infection with cytomegalovirus (CMV) occurs in over 50% of humans and can give rise to prolonged physical morbidity (e.g. chronic fatigue), it seems that this occurrence is uncommon. As a consequence, CMV cannot realistically be considered as a causal agent in CFS. For example, Straus (1993) found that only three patients in their sample of 143 fatigued patients had evidence of acute CMV infection. In contrast to this finding are studies by Hickie et al. (1990) and Wilson et al. (1989) in which current EBV infection was diagnosed in 10% and 33% of their respective samples ($N = 48$ and $N = 32$). An even higher incidence of CMV antibody levels was reported in the study by Buchwald et al. (1992); of 92 patients tested, 49% showed evidence of CMV infection. However, since the herpesviruses commonly cause latent infection after primary infection, it is not unusual for it to be reactivated and for serological tests to show elevated levels of CMV antibodies in stressed individuals and immunocompromised patients (Chase, 1991; Griffin, 1991).

The human (lymphotropic) herpesvirus type 6 (HHV-6)[4] was discovered as recently as 1986 in the blood of fatigued and immunocompromised patients (Straus, 1993). One of the most frequently cited studies investigating the possible role of HHV-6 in CFS is one conducted by

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[4] According to Ablashi (1994), HHV-6 has a prevalence rate in excess of 85% (most individuals are exposed n childhood and the virus remains latent thereafter). Reactivation has been known to occur in the face of immunologic dysfunction (Straus, 1993) and is manifested in elevated titres of IgG and IgM antibodies as well as presence of HHV-6 DNA in the lymphocytes of CFS patients. Clinical manifestations include fatigue.

Buchwald et al. (1992). Virologic investigations were performed on 259 CFS patients; the results showing reactivation of HHV-6 in 70% (compared to 20% of controls). In a recent review, Ablashi (1994) maintains that the evidence for involvement of HHV-6 in CFS is stronger than that of the other herpesviruses although the exact association between HHV-6 reactivation and CFS symptomatology remains to be established. Like EBV, HHV-6 may also affect the immune system in such a way that it leads to the reactivation of pre-existing viral conditions. The finding of HHV-6 presence in otherwise healthy subjects creates a further complication in the interpretation of causality (Straus, 1993).

(3) *Retroviruses*

The possibility that CFS may be caused or triggered by a retrovirus[5] has received some recent attention by researchers. Part of the rationale for this hypothesis is that retroviruses generally precipitate high levels of cytokines, a marker for immune activation and clinical fatigue (Bell, 1994). Although DeFreitas, Hilliard, & Cheney (1991) found HTLV-II-like viral sequences in the lymphocytes of adults and children in the Lake Tahoe outbreak (as cited in Straus, 1993), subsequent studies have failed to replicate these findings (Ablashi, 1994).

The retrovirus responsible for Borna Disease (BDV)[6] occurs naturally in horses and sheep and it has been linked to psychiatric disorders (especially depression) in humans. Significantly higher BDV seroprevalence in CFS patients (relative to controls) has been found in two recent studies (Dobbins et al., 1996; Fukuda, 1996) suggesting that BDV may play a role in some cases of CFS. Further study and explanation of the association between BDV and CFS seems warranted.

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5 Retroviruses differ from other virus types in that they merge with human DNA, which in turns directs future viral replication. Retroviruses consist of a single strand of RNA which contains the gene for an enzyme known as reverse transcriptase (this enzyme has served as a biological marker in some investigations). One characteristic of retroviruses according to Bell (1994), is that because of their ability to merge with human DNA, they are able to stay latent and undetected for long periods of time. Additionally, they may alter the host's immune response, leading to chronic activation. A final characteristic shared by retroviruses is their ability to give rise to neurological symptoms (ibid).

6 Borna disease virus can cause acute, subacute or chronic infections, producing disturbances in behaviour and cognitive functions in various animal species.

Investigations for retrovirus presence in CFS patients have been carried out in recent studies by Folks et al. (1993) and Heniene et al. (1994). Despite scanning for a wide range of human and animal retroviruses,[7] both studies failed to find evidence of retroviral markers in their groups of 26 and 21 patients respectively. These findings are not dissimilar to previous attempts (e.g. Buchwald et al., 1992). However, it appears from the literature that the laboratory detection procedures required for recovery of retroviruses are a little more sophisticated than those used for other viruses and require a high degree of precision in their use.[8] It is therefore possible that further well-controlled studies may unravel the association between retroviruses and CFS symptomatology.

In a recent review of the CFS literature, Bell (1994) suggests that the search for a viral cause or trigger in CFS continues without success. The two viruses which have been subject to the most investigations (EBV and HHV-6) have been unsuccessful in accounting for all cases of CFS; indeed, current opinion is that a yet undiscovered virus may be responsible (Levy, 1994). Similarly, at the 1995 World Meeting on CFS held in Dublin (Ireland), one of South Africa's leading virologists[9] commented that "there are thousands of viruses out there and only 15 are being tested for" (Boegman, 1995, p. 56).

1.3.2 Is CFS an Interactive Infection?

Urnovitz (1996) offers a recent view of chronic disease which questions the traditional model of an infectious disease being caused by a single agent. He suggests that although this cause and effect approach is acceptable for many infectious acute diseases, it is not able to explain

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7 These included HTLV-I, HTLV-II, HSRV and a range of retroviruses found in animals (bovine leukemia virus, feline leukemia virus, simian T-lymphotropic virus type I, gibbon ape leukemia virus and simian retrovirus types 1,2 and 3).

8 For example, Ablashi (1994) notes that laboratories using the same procedures and patients might produce different results because of increased or decreased sensitivities to detection.

9 Dr. A.N. Smith, Department of Virology, University of Natal Medical School, Durban.

more complicated biological conditions (such as CFS) where there is no definable endpoint of mortality, fever, rashes etc. He further maintains that chronic illnesses should be viewed as complex conditions in which several environmental agents (biological, chemical or radiation) may be implicated in conjunction with genetic predisposition (i.e. a host or immune suppressive gene). These host genes have only recently been discovered (1980's) and are more commonly referred to as human endogenous retroviruses (HERV's) or retrotransposons.. Their role has been demonstrated to cause an immune imbalance through the production of immunologically active peptides (retrotransposon antibodies). Urnovitz claims that the presence of retrotransposon antibodies may be a signal that an underlying chronic condition exists, and is analogous to a wound that will not heal. Of importance to this theory is the idea that retrotransposons are able to archive virus fragments as a way of creating molecular memory; the point being made by Urnovitz is that CFS is an autoimmune disease.[10] To bolster his theory, Urnovitz makes a direct connection between polio vaccines (given between 1955 and 1961 in the US) and the sudden appearance of new syndromes such as AIDS and CFS in the 1980's. Although intriguing, this theory has yet to be evaluated by the scientific community. In addition, limitations are apparent from the point of view that Urnovitz fails to consider the role of psychological factors in illness onset and course.

The idea that the onset of CFS may be associated with antibiotic use is highlighted in a recent study by Jones (1996). In a questionnaire survey, he found that the majority of his CFS sample believed that Co-Trimoxazole [Septrin] and/or Trimethoprim played a significant role in the development of their illness. In two cases, use of Septrin was found to exacerbate an existing viral condition, whereas reported side-effects included headache, allergic reactions, nausea and vomiting, malaise, joint or muscle pain, cold sweats and other CFS symptoms. Causality is difficult to establish however, given that most of these patients had also received other antibiotics and vaccines prior to symptom onset. Nevertheless, the idea that certain prescription drugs may be potentially hazardous is highlighted not only by this research but also by the fact that in the UK, Co-Trimoxazole was restricted for treatment of specific ailments as of June 1995 (ibid).

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Retrotransposons are thought to copy viral fragments from previous viral epidemics into memory in the form of host DNA (i.e. the patient's own DNA which is transmitted to offspring). Although these fragments normally remain benign, an opportunistic infection could precipitate the production of virus fragments giving rise to a range of symptoms (including fatigue).

1.4 TREATMENT ISSUES

The controversy surrounding CFS also extends to treatment. Generally speaking, treatment strategies may be separated into two broad categories (pharmacological and non-pharmacological), although this dichotomy should not be construed as an either/or approach. Indeed, composite approaches to treatment appear to have met with the highest degree of success; nevertheless, for the sake of clarity of presentation, the variety of approaches are presented here under separate headings.

1.4.1 Pharmacological Therapies

Historically speaking, the use of drugs to treat CFS arose in response to findings of viral infection and disturbed immunity during the 1980's (Gorensek, 1991). It was logical that treatment should be aimed at restoring the integrity of the immune system, and this was done via the administration of antibiotics and antiviral medications such as acyclovir, immunoglobulin injections and products designed to stimulate the immune system (e.g. liver extract and folic acid). Mixed results with regard to efficacy of such treatment is apparent in the literature (Bell, 1994; Denman, 1990; Mathews et al., 1991; Sharpe, 1991). For example, Denman suggests that while acyclovir is effective in treating post-viral fatigue of short duration, its efficacy in more chronic long term cases is unclear. A similar reservation is expressed by Mathews et al. who caution against the routine use of immunoglobulin therapy on the basis of undesirable side-effects (e.g. toxicity) and excessive cost.

Recently, Strayer et al. (1994) administered Poly(I).Poly($C_{12}U$)[11] in a randomized, multi-centre, placebo-controlled, double-blind study of 92 CFS patients. Patients who received this antiviral and immunomodulatory drug displayed improved cognition and an enhanced capacity to meet the demands of daily living (as measured by a reduction in perceived cognitive deficit and improved treadmill testing). A follow-up study on the impact of this particular drug, showed it

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[11] Poly(I).Poly($C_{12}U$) is more commonly known as Ampligen ®.

to produce specific immune regulatory effects, although the exact mechanism of action is unknown and it has yet to receive FDA approval (Suhadolnik et al., 1994). Following studies that indicated involvement of the Hypothalamic-Pituitary-Adrenal (HPA) axis, Behan, Haniffah, Doogan, and Louden (1994) administered Sertraline (a 5HT re-uptake inhibitor) on a daily basis to 79 CFS patients. Sixty-five percent of the patients were judged to be improved at the end of six months, a finding which led the authors to recommend that additional controlled studies be undertaken.

Working on the idea that CFS may be the result of a cholinergic defect, Snorrason, Geirsson, and Stefansson (1996) administered an acetylcholinesterase inhibitor (galanthamine hydrobromide) to 49 CFS patients in a double-blind design with optional cross-over (the reason for the option was that some patients refused to be without painkillers for the complete duration of the trial). Patients were assessed at baseline and at one, two, four, and eight weeks after commencing treatment; assessment consisted of a range of clinical and biochemical measures as well as psychometric tests (Spielberger State and Trait Anxiety Questionnaire, Wechsler Memory Scale and Cognitive Failures Questionnaire). Results indicated significant improvement in sleep, fatigue and myalgia at the eight-week follow-up, while improved memory and reductions in cognitive failures were also found. Unfortunately a range of side-effects (nausea, headaches, dizziness, nightmares, profuse sweating, diarrhea, vomiting, confusion and hallucinations) were found, although these tended to be dose-related. The fact that dosages required careful individual manipulation could also limit the use of this particular drug. A final point of concern in this study is that the authors were unable to specify exactly how galanthamine benefits CFS patients; nevertheless, it is a drug that appears to hold some promise in the treatment of CFS. With regard to symptomatic treatment, the use of analgesics (e.g. Paracetamol) and anti-inflammatory medications (e.g. Ibuprofen) is supported by Gorensek (1991) and Bell (1994).

The use of anti-depressants as a treatment modality for CFS also appears to be a popular option, despite reservations expressed by patients themselves. Webb and Parsons (1991) maintain that success with this treatment option is associated with the site of viral invasion and subsequent drug action (i.e. the HPA axis), while McCluskey (1993) suggests that CFS can be conceptualised as a disorder of serotonin metabolism. Tricyclic antidepressants in particular have been found to produce improvement in some patients (Bell, 1994) although it has been suggested that the

presence of undesirable side-effects necessitates close medical monitoring (Mathews et al., 1991).[12] The relatively new serotonin re-uptake inhibitors (e.g. fluoxetine) have fewer side effects and are theoretically well-suited to the treatment of depression in terms of their site of action (Wilson et al. 1994).[13] One important rationale for the use of antidepressants in the treatment of CFS is that an untreated depression could be detrimental to immunological well-being.

According to Kyle and deShazo (1992), the use of other therapeutic agents (such as interferons and interleukin-2) is currently receiving some attention by researchers, although Cotton (1991) notes that potential adverse side-effects may limit their use.

EDTA Chelation therapy represents a relatively new treatment option for CFS and it has been investigated by a local doctor and homeopath (Dr. E. Boegman).[14] In a series of studies in which 16 CFS patients were administered EDTA, it was found that all patients reported sustained improvement, with the beneficial effect reaching its peak at about three months after treatment initiation (Boegman, 1995). EDTA has seen extensive use as a treatment for improving micro-circulation; in this respect, improvement following administration to CFS patients lends some support to the theory of Dr. Simpson who believes that CFS is caused by reduced perfusion in the highly vascularised hypothalamic region of the brain.

Finally, the consumption of liquorice (which potentiates glucocorticoid hormone action) has been proposed as a treatment for CFS, although it is theoretically contraindicated in depression according to Baschetti (1995).[15] The use of liquorice has yet to receive experimental validation.

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Wilson et al. (1994) suggest that on the basis of their clinical experience, tricyclic drugs are often poorly tolerated because of sedative and anticholinergic effects.

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The pathogenesis of depression, sleep disturbance and pain is thought to include the serotonergic pathways. McCluskey (1993) suggests that a sleep disorder lies at the source of CFS symptoms and that the improvement following antidepressant drug administration is related modulation of the sleep pattern.

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EDTA acts to correct abnormalities of calcium metabolism and reduce free radicals thereby normalising antibody production, cellular immunity and enzyme activity in the cell (Boegman, 1995, p. 57).

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Baschetti notes that while patients with CFS show glucocorticoid deficiency secondary to hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis, depressed patients show the exact opposite i.e. HPA activation.

1.4.2 Non-Pharmacological Therapies

Non-pharmacological treatment modalities for CFS include psychological interventions, activity management, and so-called "alternative" treatments. These are examined separately below.

1.4.2.1 *Psychological Interventions*

There are a range of treatment options which may be considered under this heading, and they range from traditional psychotherapeutic approaches to education and lifestyle adjustments. Cognitive behaviour therapy (CBT) appears to be particularly effective according to Sharpe (1991) and Wessely, Butler, Chalder, and David (1991).[16] Relaxation training has also proved to be a useful adjunct to the treatment of CFS (Merry, 1991). Subsequent to finding evidence of symptom amplification in their group of CFS patients, Antoni et al. (1994) proposed that intervention should specifically involve techniques to modify cognitive appraisals and coping strategies.

Empirical studies documenting the efficacy of psychological interventions in the treatment of CFS appear to be in short supply. In evaluating their CBT program, Butler, Chalder, and Ron (1991) reported substantial improvement in 23 of 32 CFS patients (70%) in terms of fatigue levels and increased activity levels, although Wilson et al. (1994) found that CBT was of no specific benefit to their CFS patients. Friedberg and Krupp (1994) set out to evaluate the efficacy of CBT in three groups of individuals: a CFS treatment group (n = 22); a primary depression treatment group (n = 20); and a non-treatment control group of 20 CFS patients. Outcome measures consisted of pre-test/pos-test comparisons on the Fatigue Severity Scale, Center for Epidemiological Studies Depression (CES-D) Scale, and the Brief Symptom Inventory. Results showed that CBT led to improvement in the depressed group and was most effective for CFS patients with prominent depressed symptoms. The authors interpreted this finding by suggesting that depression is mediated by maladaptive thinking in this particular subset of CFS patients. The

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Wessely and colleagues provide a detailed breakdown of the program employed at the National Hospital for Nervous Diseases (London) and the interested reader is referred to this source for additional information.

most recent study to evaluate the efficacy of CBT is one conducted by Deale, Chalder, Marks, and Wessely (1997). These researchers employed a randomized controlled-trial design in order to assess the outcome of 13 treatment sessions of either CBT or relaxation training in 60 CFS patients. Results showed that CBT was superior to relaxation training in terms of the outcome measures used (improvement in functional impairment and fatigue ratings). Moreover, the improvements were sustained as a six month follow-up. In contrast to the more commonly used CBT approaches. Taerk and Gnam (1994) discuss the merits of a psychoanalytic treatment approach, however limited application is likely given that such approaches are likely to be labour intensive and subsequently expensive.

Abbey (1993) emphasizes the importance of including the family in treatment (especially in cases where family behaviour is suspected of reinforcing the sick role and offering secondary gain). Further, in cases of childhood and adolescent CFS, over-protectiveness has been cited as the most important family dynamic that leads to symptom perpetuation (Rikard-Bell & Waters, 1992). These authors also emphasize the efficacy of operant behavioural methods as an adjunct to cognitive behaviour therapy in this population. Using an action-research consultative approach that extended over nine months, Denz-Penhey and Murdoch (1993) devised a treatment strategy that was negotiated and developed with the patients following weekly group consultations. For example, agreement was reached in terms of group members accepting responsibility for meeting their own health needs as far as possible, in gaining control of symptoms, and modifying their individual lifestyles. The result of this pilot study was successful in terms of the identification of a service delivery model acceptable to both patient and practitioner; however outcome was not evaluated in this study.

1.4.2.2 *Activity Management*

The use of graded exercise programs in CFS management is advocated by most practitioners although it is not without controversy (Sharpe, 1991; Woods & Goldberg, 1991). Certainly, it is a legitimate form of treatment for many medical disorders and the beneficial effects of exercise on mental and physical well-being is widely acknowledged (Ornstein & Sobel, 1987). However, since there is a danger of symptom exacerbation following exercise in CFS patients, this

treatment regime requires careful implementation and monitoring (Smith, 1991). To some extent, exercise in CFS is a double-edged sword; too much or too little activity can worsen symptomatology. According to Peters (1996), the precise mechanisms for the complex relationship between beneficial and detrimental exercise are not clearly understood. Weight (1996) suggests that it is important to recognise that rather than being a linear relationship, exercise and immunity are best conceptualized in terms of a *"J"* shaped curve, where moderate exercise has an enhancing effect, but where excessive exercise increases illness susceptibility. In CFS patients, it could be that the threshold for a detrimental effect of exercise is much lower than that of healthy individuals. Despite the unpredictable effects of exercise in CFS patients, Denman (1990) reports the favourable outcome of the graded exercise program used at a Middlesex hospital, while Bell (1994) reports that physiotherapy (especially passive stretching exercises) is beneficial to some CFS patients. Water-based exercise programs are recommended by Kyle and deShazo (1992). In terms of the time span over which a graded exercise regime might operationalised, there seems to be agreement that physical reconditioning should be graded and with activity levels being increased gradually over time (Sharpe, 1991). In conjunction with an exercise program, the importance of a frequent rest periods during the day is endorsed by a number of CFS practitioners. However, both Smith (1991) and Bell (1994) emphasizes the importance of individualised activity management programs since what might work well for one patient may be detrimental to another.

Some attention has been directed to the exercise programs of athletes with CFS (Budgett, 1991). Treatment principles are largely the same as those for more sedentary individuals although Budgett suggests that athletes may need to be convinced to exercise in a non-competitive manner.

1.4.2.3 *Alternative Treatments*

The use of so-called "alternative" treatment modalities for CFS patients has also been reported in the literature. Possibilities in this regard include acupuncture, yoga, meditation, use of visual imagery, herbal remedies, antifungal agents, reflexology, homeopathy, spiritual healing, aromatherapy and dietary manipulation.

With regard to nutrition, dietary deficiencies have been identified in some CFS patients (Stewart, 1991); in this respect Gorensek (1991) recommends a high-fibre, low-fat balanced diet. An exclusionary approach to foodstuffs which may exacerbate symptoms or cause allergies, is recommended by Merry (1991). Specifically, it has been suggested that the consumption of sucrose, foods high in refined carbohydrates, tea, coffee and alcohol may worsen CFS symptoms (Stewart, 1991). The efficacy of vitamin and mineral supplements in alleviating CFS symptomatology is unproven although low levels of zinc and magnesium in CFS patients have been reported in some patients (ibid). The administration of essential fatty acids (e.g. evening primrose oil) as well as co-enzyme Q10,[17] and L-carnitine (another mitochondrial stimulant) have also been reported as having a beneficial effect in some patients (Bell, 1994). However, the local medical profession is somewhat sceptical about the efficacy of such treatment (Reader, W.J. - personal communication, April 1994).

More controversial treatments which are considered to be potentially dangerous include the extraction of dental fillings, colonic irrigation, total exclusion diets, long-term antibiotic therapy and hypnosis (Blondel-Hill & Shafran, 1993), although this view is not shared by Leyton (1993) who believes that alternative therapies may serve to empower patients and indirectly assist recovery.

1.4.3 Composite Approaches

Hatcher (1994) describes a multi-disciplinary "Fatigue Clinic" in which treatment revolves around advice on lifestyle management and antidepressant therapy. Specialist input is given by a consultant in infectious diseases, a liaison psychiatrist and an occupational therapist. Both group-based and individual interventions are offered; group sessions are run by the occupational therapist and include discussions on "gradual increases in activity, diet, exercise, stress and relaxation techniques, the impact of CFS on personal relationships and feelings, and coping with problems with memory and concentration" (p. 112). Recently, occupational therapists at the

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17 According to Goldstein (1993), this is a necessary co-factor in mitochondrial oxidative phosphorylation.

Havering Hospital's Trust in the UK have devised an inpatient management program based on principles of OT lifestyle management and modified cognitive behavioural techniques ("CFS Management,"1996). Inpatient treatment lasts from three to nine weeks and is followed by an eight week program of outpatient group sessions, PT and counselling (see also section 1.2.6)

To conclude this section on treatment issue, it would appear from the literature that there is no one specific treatment for CFS. In this regard, Murray (1992) believes that our failure to find an effective treatment strategy stems from our lack of knowledge about etiology and pathophysiology. Wilson et al. (1994) suggest that the lack of specificity in the treatment of CFS encourages pseudoscience, but that this can be circumvented through the use of a biopsychosocial (i.e. composite) approach in a multi-disciplinary setting. Medical and psychological evaluations are recommended as integral components of such an approach. There appears to be at least some support for the efficacy of cognitive behaviour therapy (Deale et al., 1997; Friedberg & Krupp, 1994), while a graded exercise regime has also been recommended as part of an overall treatment strategy (Denman, 1990).

1.5 THE NATURE OF FATIGUE

There can be little doubt that patients with CFS experience a sense of fatigue. What is less clear is the nature of this subjective fatigue. Is it synonymous with weariness, having no energy, tiredness or exhaustion? Should it be defined in behavioural, phenomenological, or biological terms? The literature reveals that emphasis is placed on different aspects by different investigators. Despite this variation, there is increasing support for the view that fatigue is a continuous dimension comprised of all three of these components (Chalder et al., 1993). Consequently, the more recent fatigue scales are multidimensional in their scope (Bentall, Wood, Marrinan, Deans, & Edwards, 1993; Fisk et al., 1994; Vercoulen et al., 1994). For example, Vercoulen and his colleagues assembled a 24-item questionnaire that included items designed to measure behavioural, emotional, social and cognitive aspects of CFS. However, these researchers made no attempt to investigate the psychometric properties of their instrument, thereby limiting its application. Other fatigue scales that have appeared in the literature include a 13-item fatigue questionnaire used by Wessely and Powell (1989); this instrument consisted of eight items measuring symptoms of physical fatigue and five items measuring mental fatigue. A modification of this questionnaire was subsequently used in studies by David et al. (1990) and Chalder et al. (1993). Additional fatigue questionnaires reported in the literature include those used by Bentall et al. (1993), Vercoulen et al. (1994) and O'Dell et al. (1996), although reliability was not addressed in any of these studies. The best instrument to date appears to be the Fatigue Impact Scale (FIS) devised by Fisk et al. (1994). The FIS is a comprehensive 35-item self-report instrument in which respondents are asked to rate the extent to which fatigue has caused problems for them in relation to various physical, cognitive, and social behaviours. While such instruments appear to hold promise for the assessment of fatigue in CFS, their clinical utility awaits verification from other researchers. Unfortunately, the FIS was not available for use at the inception of the current study.

A further point of conceptual difficulty lies in the experience of fatigue. It is evident that fatigue may be a component of a variety of different medical and psychiatric disorders; what is less clear is whether the experience of fatigue differs from one condition to another. For example, does the fatigue experienced by someone with a debilitating medical condition (such as leukemia) differ from that of CFS? This question remains unanswered at the present time. Given that the

concept of fatigue defies simplistic explanation, one solution may be to view it as an emergent biological property that results from over-exertion. From a definitive perspective however, fatigue is traditionally conceptualized as being either physical or psychological in origin. The physical dimension of fatigue has received more attention because it is easier to measure objectively using laboratory procedures (Chalder et al., 1993). However, this dichotomy between physical and psychological fatigue is somewhat simplistic if not artificial. Recent conceptualizations of fatigue are global in definition and recognize that physical and psychological fatigue are essentially two sides of the same coin. For example, Barofsky and Legro (1991) define fatigue as "an overwhelming sustained sense of exhaustion and decreased capacity for physical *and* mental work" (p. 95). Fatigue can result from a range of different activities, both pleasurable and non-pleasurable; furthermore it can develop over seconds, minutes, hours or even months (Craig & Cooper, 1992). These authors argue that such diversity in cause and effect prevent the conceptualization of fatigue in a single unifying theory or account. In keeping with tradition, this brief review of literature also attempts to examine fatigue along the physical/psychological dimension although it should be noted that discussion of the physical dimension has been held over for discussion in Chapter 3 where it is more appropriately addressed within the context of muscle physiology.

1.5.1 Psychological (Mental) Fatigue

Since most definitions of fatigue consider both physical and psychological fatigue as being inter-related, it is difficult to specify exactly what constitutes psychological fatigue. However, recent studies in cognitive psychology give us some framework for assessing psychological or mental fatigue.

The most popular method for investigating mental fatigue has been to engage a subject in a vigilance or mental task until a performance decline is noted (Craig & Cooper, 1992). Declines in attention and concentration can be measured in terms of selectivity and capacity of attention as well as susceptibility to distraction (Kennedy, 1988). Experiments employing this strategy have a long history in psychology. As early as 1928, Poffenberger reported subject performance output for five and a half hours of continuous engagement on four tasks; digit addition, sentence

completion, composition judgement and an intelligence test (as cited in Craig & Cooper, 1992). He found that performance remained stable for about two hours after which there was selective decline in the digit addition task; in contrast, sentence completion and composition judgement remained the same while intelligence test output increased. Of interest to Poffenberger was the finding of a discrepancy between performance on these tasks and a subjective rating of fatigue assessed at 20 minute intervals (these ratings declined steadily throughout from "extremely good" to "extremely tired"). Other studies of mental fatigue have investigated factory workers on long shifts, fighter pilots during WWII and driving behaviour (Craig & Cooper, 1992). All show that performance declines in the face of prolonged or excessive mental activity.

Electrophysiological paradigms have also been used in the study of fatigue. Gevins et al. (1990) investigated the effects of sustained mental work on brain topography (event-related covariance analysis or ERC's). The study required subjects to make cognitive discriminations and fine motor responses to a visual memory task. Results indicated that changes in the electrical activity of the brain are discernible long before performance deteriorates. These changes were maximal in the frontal regions (a part of the brain responsible for motor preparation and response inhibition). The authors concluded that ERC's have great potential as an early warning device to signal impending mental fatigue, although this particular measure has not yet been applied to the study of CFS. Other recent studies on arousal and vigilance (reviewed by Kennedy, 1988) have demonstrated that engaging a subject in repetitive tasks leads to lowered arousal and distractibility, with an accompanying increase in performance errors. On the other hand, increased emotional arousal is known to facilitate attentional selectivity. In this regard, Kennedy (1988) hypothesizes that the emotional reaction to fatigue may consist of irritability, complaints of somatic symptoms (e.g. headache) and a tendency to take risks; these in turn, he argues, represent a homeostatic mechanism intended to maintain arousal but at the expense of a decrement in performance. Although the complex relationship between emotionality, arousal and cognition has been the subject of some recent debate, the way in which these variables interact with fatigue remains unclear (ibid).

Of interest in these and other studies, is the possibility that fatigue may set in as a result of boredom and reluctance to continue with a task rather than being due to any real decline in physical or mental resources (Craig & Cooper, 1992). For example, after finding that their CFS

patients failed simple tasks but got successive (and more difficult) tasks correct, McDonald et al. (1993) suggested that patients with marked fatigue may find any task, irrespective of level of difficulty, a problem to initiate. This is the opposite to the pattern one might anticipate in fatigued states where performance might be expected to decline over repeated trials (i.e. competent behaviour becomes degraded over time). Whatever the explanation for this finding, it highlights the importance of seeing the psychological, physical, and behavioural components of fatigue as being inter-related. This makes the study and understanding of chronic fatigue syndrome a complex undertaking.

Unfortunately, there have been few attempts to unravel the relationship between mental and physical fatigue in CFS. Wessely and Powell (1989) found that while physical fatigue is as common in CFS as it is in depressive and neuromuscular disorders, this is not true of mental fatigue, which although occurs with similar frequency in CFS and depression, occurs only in neuromuscular disorders when there is co-existing psychiatric illness.

One recent and intriguing view of chronic fatigue is that it is a non-specific entity that represents a generalized response to stress, extended over a period of time (Craig & Cooper, 1992). In this view, chronic fatigue syndrome could be conceptualized as a kind of burn-out phenomenon. Although direct parallels between CFS and burn-out are lacking in the literature, Morakinyo (1980) described a "brain-fag syndrome" following intensive study periods in a small group of African students. The syndrome was characterized by fatigue, sensory disturbances, diminished intellect and emotional disturbance; Morakinyo suggested that stress (as well as neuroticism) played an etiological role.

1.6 CURRENT STATUS OF CFS

Although the cause of CFS has not yet been established, the current conceptualization of the disorder is that it exists as a complex interaction of cerebral dysfunction, trigger factors, psychological factors and social attitudes (Thomas, 1993). There can be little doubt that CFS is associated with a compromised immune system and it is widely accepted that the immune system is chronically activated in CFS patients. Most authors also agree that CFS represents a spectrum of disorders in which there may be a variety of physiological and psychological precipitant and maintaining factors. Again, it is possible that these physiological and psychological variations exist on a common dimension.

A revised CFS case definition was finally released by the CDC in 1994 (Fukuda et al., 1994). The revision was the result of international cooperation, since one aim was to consolidate different international approaches by developing a conceptual framework and a set of research guidelines (Fukuda, 1996). Modifications of the 1988 criteria include a listing of recommended evaluation tests, common diagnostic differentials, and a reduction of the number of symptoms required to meet the diagnostic criteria. All physical signs were dropped from the inclusion criteria as it was felt that "their presence had been unreliably documented in past studies" (Fukuda et al., 1994, p .957). In addition, the requirement for a 50% reduction in daily activity was dropped from the revised set of criteria because of difficulties in verifying this particular criterion. The revised case definition allows for sub-grouping of unexplained cases of chronic fatigue. However, this sub-grouping appears to be done only after certain conditions have been excluded. Examples of conditions that do not warrant a diagnosis of unexplained chronic fatigue, include: medical conditions such as untreated hypothyroidism, unresolved cases of hepatitis B or C virus infection, bipolar affective disorder, severe obesity, and a recent history of substance abuse. On the other hand, conditions which do not exclude a patient from the diagnosis of unexplained chronic fatigue include: fibromyalgia, anxiety and somatoform disorders, depression, Lyme disease, and multiple chemical sensitivity disorder. Once the unexplained cases of chronic fatigue have been clinically evaluated, they are categorised as either cases of chronic fatigue syndrome or idiopathic chronic fatigue on the basis of the criteria presented in Table 1-11.

Table 1-11. Revised CDC Criteria for Chronic Fatigue Syndrome

Classify as chronic fatigue if:

(a) criteria for severity of fatigue are met (i.e. self-reported, persistent fatigue lasting 6 or more consecutive months); and

(b) four or more of the following symptoms are concurrently present for ≥6 months:

1. impaired memory or concentration
2. sore throat
3. tender cervical or axillary lymph nodes
4. muscle pain
5. multi-joint pain
6. new headaches
7. unrefreshing sleep
8. post-exertion malaise

Classify as idiopathic fatigue if fatigue severity or symptom criteria for chronic fatigue syndrome are not met.

(Fukuda et al., 1994, p. 956):

According to the revised criteria, a case of *chronic fatigue syndrome* is defined by the presence of:

(1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social or personal activities; and

(2) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue: self reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain, multi-joint pain without joint swelling or redness; headaches of a new type, pattern or severity; unrefreshing sleep; and post-exertional malaise lasting more than 24 hours.

A case of *idiopathic chronic fatigue* (IDF) is defined as clinically evaluated, unexplained chronic fatigue that fails to meet criteria for the chronic fatigue syndrome. The CDC suggest that the reasons for failing to meet the criteria should be specified. As a guideline to researchers, the CDC recommend that cases of CFS and IDF be sub-grouped according to variables such as: identifiable neuropsychiatric condition, current level of subjective and objective fatigue, duration of fatigue and current level of overall functional performance (as might be measured by instruments like the Sickness Impact Profile). Epidemiologic or laboratory profiles (such as presence of a specific immunologic marker) may also be used to stratify study samples.

It is too soon to comment on the utility of the revised criteria as no evaluative or comparative studies had been completed at the time of writing this literature review. However, Fukuda et al. (1994) note that in conceptualising the revised criteria, the CDC acknowledged that disagreement occurred between those favouring a more restrictive approach (i.e. using several symptom criteria) and those who wanted a broader definition (exemplified by the Australian and British/Oxford CFS case definitions).

Recently, Brussels was the venue for the First World Congress on Chronic Fatigue Syndrome and Related Disorders (November 9-11, 1995). The first dedicated CFS journal (*Journal of Chronic Fatigue Syndrome*) was also launched in 1995; the major aim being to foster interdisciplinary research. It is difficult to make predictions about the direction that future research into CFS might take. Until a firm etiological basis has been established, treatment will no doubt remain non-specific and trend-determined. Unfortunately, the scientific debate which occupies a significant portion of the literature does not assist the fatigued patient who wants answers and seeks a cure. From a patient perspective, up-to-date information and advice on CFS is now freely available on the Internet; one website, the Cheney Clinic Information Service (CCIS), is described as "an accessible information and consultation service with current information on the diagnosis, management and other services related to CFS".[18]

18

The address for this website is [http://www.fnmedcenter.com/ccis]. Current scientific news on CFS can be found in ONLINE NEWS at [http://www.calypte.com/online/index.html].

CHAPTER 2

CHRONIC FATIGUE SYNDROME, PSYCHOPATHOLOGY, AND PSYCHONEUROIMMUNOLOGY

"The essential issue is whether it is possible to strike a sensible balance between psychological factors and biological factors in the understanding and management of disease" (Cousins, as cited in Ballieux, 1994, p. 387).

The idea that CFS can in part be attributed to psychological or psychiatric causes, forms a significant part of the CFS literature. Eisenberg (1988) was one of the first to suggest that chronic viral infection could be considered as a somatic presentation of personal distress. Later, Abbey and Garfinkel (1990) argued that CFS represents a culturally-sanctioned form of illness behaviour and that most of its sufferers have an identifiable psychiatric disorder (usually depression). Such connectivity is hardly surprising given the historical accounts of neurasthenia (with frequently implied hysteria and neurosis) and the more recent failure to identify a single, biologically-based etiological agent. However, as Jenkins (1991) succinctly points out, "the presence of psychological symptoms is not, in itself, an argument for the functional nature of the illness" (p. 962). It could be, for example, that psychological symptoms may have preceded the illness or contributed to its onset and persistence; likewise, disabling fatigue and the various symptoms of CFS could precipitate the emergence of reactive psychological symptoms. Such reasoning is of course not new; in her review of depression in medical illness, Ray (1991a) notes that "historically, many disorders have at one time or another been conceived of in psychological terms, with this model being abandoned when a somatic cause has been identified" (p. 3).

At least part of the functional versus organic debate (according to Rikard-Bell & Waters, 1992) centres around the argument about whether fatigue is a physical or psychological symptom. Some authors have highlighted the limitations inherent in categorising CFS as an either/or entity in terms of a functional/organic dichotomy, and called for a more multifactorial (biopsychosocial)

approach that acknowledges the interactions between psychological and physical influences on health (David, 1991; David et al., 1988; Kaplan et al., 1992; Tannock, Costa, & Brostoff, 1994; Ware, 1993). As early as 1988, David and colleagues commented that "partisan viewpoints have contributed little to illuminating the pathogenesis and treatment of the postviral fatigue syndrome and have added to patients' distress" (p. 698). More recently, Taerk and Gnam (1994) examine the limitations in viewing CFS as a simple cause and effect model. Despite these calls for a more integrated approach, the debate as to whether CFS is best conceptualised as an organic or functional illness continues.[19] This section of the literature review examines the basis for this ongoing dialogue and introduces the relatively new field of psychoneuroimmunology, a discipline which has obvious significance for an informed understanding of CFS.

2.1 CHRONIC FATIGUE AND PSYCHIATRIC ILLNESS.

As mentioned elsewhere in this dissertation, there appears to be general agreement that CFS is characterized by immune system dysfunction which in turn, is triggered by viral infection in at least some cases. At the same time however, the role of psychological factors must be acknowledged and integrated in a multi-factorial view of CFS. Acknowledgement of both organic and psychological factors in CFS is a point emphasised by Ray (1991a) who suggests that these factors may be interactive rather than additive (i.e. the contribution of any one particular factor will depend on the presence/absence of the other factors). He also suggests that these variables may have a reciprocal influence on each other, resulting in an enhanced state of somatic and psychological dysfunction (i.e. a "vicious circle" scenario). An added complication for researchers is that other variables such as social adversity, have to be considered in order to gain a full understanding of the processes involved.

19

While the writer endorses the sentiment expressed in these reservations, the use of the organic-functional dichotomy is a useful way of organising and discussing relevant research findings and is the approach used to systematize and facilitate discussion in Chapters 2 and 3 of this thesis. Nevertheless, it is recognized that the separation of the material into psychological and biological aspects imposes a somewhat limited and artificial conceptual framework on data which is essentially multidimensional.

The importance of assessing psychiatric symptoms in CFS exists not only at a differential diagnostic level, but also at the level of the extent to which a concurrent or reactive psychiatric condition might contribute to compromised immunity and hence increased susceptibility to viral illness. Although Kendell wrote about psychiatric complications in two of his female patients as early as 1967, Taerk et al. (1987) were one of the first groups of researchers to describe the comorbidity of psychological symptoms in CFS patients. Subsequently, there has been general acceptance of a high incidence of psychological conditions in CFS (Kyle & deShazo, 1992; Wessely, 1991), with estimates ranging from 29% to 80% of affected patients (Manu, Lane, & Mathews, 1989). While a range of pathologies have been associated with CFS, depression appears to be the most common although anxiety and somatization disorders are also well-represented. Table 2-1 (pp. 83-87) summarises the findings of representative studies from the CFS literature.

The notion that CFS tends to occur in individuals with a premorbid vulnerability to depression and other psychological conditions has been supported by some (Kruesi, Dale, & Straus 1989; Manu et al., 1989; Stricklin, Sewell, & Austad 1990; Taerk et al., 1987) but not all studies (Hickie et al., 1990). Hickie and colleagues have promoted the idea that psychological disturbance is more likely to be a consequence of CFS rather than an antecedent. Some support for this viewpoint comes from studies that have found an absence of psychiatric symptoms in 25 -35% of CFS patients (Krupp et al., 1991). On the other hand, Manu, Mathews, and Lane (1991) looked at the frequency of panic disorder in CFS patients and found it to be 10 time more prevalent than in the general population (a finding they interpreted as support for the psychiatric vulnerabilities of CFS patients).

Table 2-1. Studies Investigating Psychological/Psychiatric Aspects of CFS

Author(s) and date	Patient type, number, and controls	Diagnostic instruments	Psychiatric findings
Kendell (1967)	2 case studies of benign ME	Clinical assessment only	Both cases showed evidence of agitated depression; one showing marked aggression and suicidal tendencies, while the other displayed a combination of generalized and hysterical seizures.
Taerk et al. (1987)	24 "neuromyasthenics" 24 controls	DIS, BDI, dexamethasone suppression test	Major depression (DSM III-R criteria) diagnosed in 67% of cases and 29% controls (16 of the neuromyasthenics had BDI scores of 9 or more).
Manu, Mathews, and Lane (1989)	100 patients with fatigue of greater than 6 months duration	DIS, BD	44% patients met criteria for depressive illness in past 6 months, while 24% were currently depressed. 15% remainder met criteria for other psychiatric disorders (e.g. somatization disorder, panic disorder, social phobia) currently present or present in 6 months prior to evaluation.
Manu, Lane, and Mathews (1989)			Somatization disorder diagnosed in 15% (see text for details)
Wessely and Powell (1989)	47 CFS patients, 33 neuromuscular controls, 26 depressed controls	RDC, SADS, GHQ-12, HAD, Somatic Discomfort Questionnaire, Fatigue Questionnaire, Symptom Attribution Questionnaire	Using Research Diagnostic Criteria, psychiatric diagnoses found in 72% of patients (versus 36% controls). Previous psychiatric history evident in 43%. Breakdown of current diagnostic categories: 47% major depression; 15% somatization disorder; phobic disorder in two patients; and one patient in each of the following categories - generalized anxiety disorder, conversion disorder, and minor depression.

Table 2-1 (continued). **Studies Investigating Psychological/Psychiatric Aspects of CFS**

Author(s) and date	Patient type, number, and controls	Diagnostic instruments	Psychiatric findings
Kruesi et al. (1989)	28 CFS patients	DIS, DSM III	Psychiatric diagnosis made in 75% (*N*=21) with 36% of patients revealing history of a psychiatric condition (anxiety, depression or alcohol abuse) that preceded the onset of fatigue. Current diagnoses were depression in 55% of women and 25% of men. A further 25% met the criteria for dysthymia, phobias (32%), and somatization disorder (10%).
Hickie et al. (1990)	48 CFS patients, 48 depressed controls	SCID-P, DSM-III-R, EPI, Zung Self-Rating Depression Scale, IBQ, HAM-D,	24% CFS patients currently depressed (compared to 13% of controls). Premorbid prevalence of major depression found to be 13%, and total psychiatric disorders 25% (compared to 90% of psychiatric controls).
Valdini, Steinhardt, and Feldman (1989)	22 CFS patients	SCL-90-R	A high incidence of psychopathology was evident; the number of individuals scoring above the 95 percentile were: phobic anxiety (4); paranoid ideation (6); somatization (6); anxiety (9); psychoticism (11); hostility (11); obsessive-compulsive (13); and depression (15).
Gold et al. (1990)	26 CFS patients (EBV positive), 18 healthy controls	DIS, DSM III	42% CFS group found to be depressed (compared to none of the controls). 50% experienced major depression just prior to CFS onset while a further 73% had a lifetime prevalence of major depression (compared to 22% controls). More somatic symptoms were reported by CFS patients (9.7 versus 1.1); they also scored above the 60th percentile (when compared to psychiatric patients) in terms of their DIS global symptom index. The highest scores were depression (67th percentile) and somatization (65th percentile).

Table 2-1 (continued). **Studies Investigating Psychological/Psychiatric Aspects of CFS**

Author(s) and date	Patient type, number, and controls	Diagnostic instruments	Psychiatric findings
Yeomans and Conway (1991)	15 CFS patients	HAD, MADRS, PSE	93% had MADRS rating of mild depression. A positive HAD rating of depression and anxiety was found in 33% and 27% respectively. On the PSE 13% received a diagnosis of depression while 20% met the criteria for phobic illness. Analysis of premorbid history failed to reveal evidence of psychiatric disorder, although three patients had a history of school refusal and another reported a life-long bird phobia.
Manu et al. (1991)	200 CFS patients	DIS, DSM-III-R	26 patients (13%) fulfilled the diagnostic criteria for panic disorder PD (panic attacks also preceded the onset of CFS in 50% of this group). Comorbidity with other psychiatric conditions noted in 20 PD patients while 65% had current major affective disorder. A high frequency of somatization disorder was also found in the PD patients.
Wood et al. (1991)	34 CFS patients, 24 neuromuscular controls	PSE, CATEGO, Hospital Anxiety and Depression Scale, STAI	41% CFS patients met criteria for current psychiatric illness (24% depression, 18% anxiety disorders, 6% somatoform disorders) compared to 13% of controls. In addition, premorbid history of the CFS patients revealed a previous psychiatric condition in 27%, with 32% reporting a stressful life event in the six months prior to symptom onset.
Mathews, Lane, and Manu (1991)	35 EBV patients, 35 fatigued but non-EBV patients	DIS, Rand Vitality Scale, State Anxiety Inventory, BDI, SCL-90, Schedule of Recent Experience.	Psychiatric morbidity found in both groups, with an incidence of 74% and 71% (experimental versus control). Mood, anxiety, and somatization disorders the most common DIS diagnoses but no group differences were evident. SCL-90 criteria for positive case definition met in 44% and 52% respectively, with depression being the most prominent symptom. Elevations in anxiety and depression were found for both groups.

Table 2-1 (continued). **Studies Investigating Psychological/Psychiatric Aspects of CFS**

Author(s) and date	Patient type, number, and controls	Diagnostic instruments	Psychiatric findings
Hickie, Lloyd, and Wakefield (1992)	33 CFS patients	SCID, DSM-III-R, HAM-D	7 patients (21%) met DSM-III-R criteria for major depression, while the HAM-D suggested that the group as a whole was mildly depressed mean score of 10.6).
Vercoulen et al. (1994)	298 CFS patients (comparisons were made with published test data)	BDI, SCL-90-R, SIP	On the SCL-90-R CFS patients were found to differ significantly from psychiatric out-patients, functional bowel disorder patients, and healthy subjects (they were more dysfunctional on all subscales). On the BDI 36% had scores indicative of clinical depression (score ≥ 16) although 32% reported no depressed symptoms whatsoever. With regard to the SIP, CFS patients reported more problems in social interactions.
Pepper et al. (1994)	69 CFS patients 65 multiple sclerosis (MS) controls, 25 depressed controls	MCMI-II, Centre for Epidemiological Studies Depression Scale (CES-D), SCID, Fatigue Severity Scale (FSS).	CFS patients reported higher rates of current depression than MS patients (23% versus 7%) but lower than depressed controls. The FSS failed to reveal any differences between the CFS and MS patients although in comparison to the depressed group, the CFS patients had significantly elevated fatigue severity. Although CFS patients had less MCMI-II Axis I and Axis II symptoms than depressed patients, their profiles were similar to the MS patients.
Schweitzer et al. (1994)	40 CFS patients (comparisons were made with published test data)	IBQ, GHQ-28, BDI	67% of CFS patients classified as psychiatric case-positive on the GHQ. They also scored higher than general practice controls on the IBQ subscales of General Hypochondriasis and Disease Conviction but lower on the Psychological/Somatic subscale. No difference was noted between the CFS group and published data for psychiatric patients in terms of hypochondriasis.

Table 2-1 (continued). **Studies Investigating Psychological/Psychiatric Aspects of CFS**

Author(s) and date	Patient type, number, and controls	Diagnostic instruments	Psychiatric findings
Cope et al. (1995)	26 CFS patients, 13 depressed patients, 18 healthy controls	BDI, STAI	No difference between depressed group and depressed CFS individuals in terms of BDI-measured depression. On the STAI, both the depressed group and depressed CFS patients scored significantly higher than the non-depressed CFS and healthy groups.
Johnson et al. (1996)	42 CFS patients; controls consisted of 18 MS, 21 depressed, 32 healthy individuals	DIS, DSM-III-R	Significantly more CFS subjects met the diagnosis for somatization disorder than any of the control groups when a full set of somatization symptoms were used in the assessment. However, when five additional diagnostic variations were used to classify the symptoms, fewer group differences emerged.
Egle, Nix, and Schwab (1996)	40 CFS patients	SCL-90-R, Giessen Beschwerdebogen (GBB)	Significant elevations were found for the somatization, depression, anxiety, obsessive-compulsive and global symptom index (GSI) scales of the SCL-90-R.
Katz and McDonald (1996)	87 referred patients (45 meeting CDC criteria)	SCID and semi-structured interview	A history of mood disorder found in 47% (with family history in 20%); anxiety disorder in 9%.

Key to abbreviations:

BDI - Beck Depression Inventory, CATEGO - a computerized diagnostic system, CIS-R - Revised Clinical Interview Schedule, DIS - Diagnostic Interview Schedule, DSM-III and DSM-III-R - Diagnostic and Statistical Manual of the American Psychiatric Association (3rd edition and revised edition), GBB - Giessen Beschwerdebogen (includes fatigue scale), GHQ - General Health Questionnaire, HAD - Hospital Anxiety and Depression Scale, HAM-D - Hamilton Rating Scale for Depression, IBQ - Illness Behaviour Questionnaire, ICD - International Classification and Diagnostic System, MCMI - Millon Clinical Multiaxial Inventory, MMPI - Minnesota Multiphasic Personality Inventory, POMS - Profile of Mood States, PSE - Present State Examination, SADS - Schedule for Affective Disorders and Schizophrenia, SCL-90 and SCL-90-R - Symptom Checklist 90, SIP - Sickness Impact Profile, STAI - State and Trait Anxiety Inventory, MS - multiple sclerosis.

More recently, Katon and Walker (1993) report on a large mental health survey conducted in the USA in which the relationship between unexplained fatigue and psychiatric diagnoses was explored in a large sample of 18,751 people who were given structured psychiatric interviews. Results showed a strong positive correlation between reported lifetime fatigue[19] in both men and women and prevalence of major depression, dysthymic disorder, panic disorder and somatization. Respondents with current fatigue also reported a significantly greater number of medically unexplained symptoms than those not currently fatigued. Katon and Walker compared their findings with a study by David in which approximately 10% (77) of 770 primary care attenders reported being chronically fatigued (as cited in Katon & Walker, 1993). Of these, 40% had a personal history of psychiatric illness[20] with 43% reporting a family history of psychiatric illness. The Clinical Interview Schedule (CIS) identified 49% of the 77 fatigued patients as fulfilling the CIS criterion for psychiatric caseness. In a subsequent study of 686 primary care patients, McDonald et al. (1993) correlated measures of fatigue, psychiatric morbidity and social stress. They found that while psychiatric symptomatology and fatigue were related, the strength of the correlation was modest at .39.

Is CFS a form of somatization disorder or malingering? High prevalence rates of somatization disorder in CFS have been found in some studies (Gold et al. 1990; Manu et al., 1991; Wessely & Powell 1989) but this has not been a universal finding (Hickie et al., 1990; Wood et al 1991). Using the Diagnostic Interview Schedule (DIS), Manu,Mathews, et al. (1989) set out to investigate the relationship between chronic fatigue and somatization disorder in 100 fatigued outpatients (see Table 2-1). A prevalence rate of 15% emerged (13 of 35 symptoms needed to reach the diagnosis) and eight symptoms were found to differentiate these patients from the others (pain in extremities, joint pain, other pain, shortness of breath, chest pain, blurred vision, muscle weakness or paralysis, and sexual indifference). One difficulty of interpretation of studies such as this is that somatization disorder may masquerade as a disguised or masked

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Lifetime fatigue was defined as "medically unexplained fatigue occurring for a minimum duration of two weeks at some point in the patient's life" (p. 195)

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Criteria not specified; presumably based on history of psychiatric consultation/treatment.

form of depression (Ray, 1991). In this respect, the diagnosis of somatization is, to some extent, an umbrella term that covers a wide range of clinical behaviours and includes not only patients who present with apparent physical symptoms despite demonstrable emotional distress, but also those patients who believe they are ill in the absence of supporting medical evidence, i.e. those who are malingering (Abbey, 1993). It has been argued by Bell (1994) that CFS is neither somatization disorder or malingering. He suggests that while symptom variability may accompany somatization disorder and malingering, this is likely to be a random event; in contrast, the symptoms in CFS are generally not random (i.e. CFS patients describe their symptoms in a similar way).

In reviewing these studies, interpretation is hindered by the variation in research design and methodology. Some studies have failed to use appropriate controls (e.g Stricklin et al. 1990; Taerk et al. 1987) thereby limiting their conclusions. At a more fundamental level, there is some evidence of variation in the use of terminology used to describe CFS patients (especially those studies conducted prior to the widespread acceptance of the CDC criteria; e.g. Kruesi et al., 1989; Taerk et al., 1987). This makes a comparative evaluation difficult. For example, in the Manu et al. (1989) investigation of somatization disorder, the fatigued patients used in the study were selected on the basis of "feeling tired at least half the time for at least the past month" (p. 389). In addition, while most studies reviewed used the CDC criteria, some (e.g. Yeomans & Conway, 1991) used the Oxford/British Criteria. It is therefore possible, as Gold et al. (1990) suggest, that psychiatric prevalence depends on the methods and criteria used; in this respect, marked inter-study variability is evident. Furthermore, concordance between clinical impression and psychometric instruments is not always demonstrated. To this extent, Gold and his colleagues have suggested that psychometric questionnaires tend to over-emphasize specific psychiatric syndromes rather than non-specific distress and that where possible, this approach should be integrated with clinical assessment.

In seeking to overcome the methodological problems apparent in previous estimates of somatization disorder in CFS, Johnson et al. (1996) adopted more stringent selection criteria[21] for

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Only patients who met CDC criteria at the time of intake and who had no psychiatric history in the previous 5 years preceding CFS onset were included.

their CFS patients, employed appropriate comparison groups and used both objective and subjective assessment methodologies (see Table 2-1). Their study found that the terminology used to define somatization disorder was a determinant of the number of individuals who met the diagnostic criteria; for example, few patients fulfilled the DSM-III-R criteria for somatization disorder compared with those who met the Diagnostic Interview Schedule (DIS) criteria.

Although literature exists highlighting the importance of personality traits in the duration of viral conditions such as the common cold (Chase, 1991), only three studies appear to have specifically investigated personality profiles in CFS patients. The first is one by Millon et al. (1989) in which the MCMI-II was administered to 24 CFS patients. Scale elevations above a *BR*75 cut-off were found for *Histrionic* (33% of patients), *Schizoid* (29%), and *Avoidant, Narcissistic* and *Aggressive* subscales (each 25%). For the severe personality pathology scales, three subjects (12.8%) exceeded a *BR*75 cutting score on the *Borderline* scale. These findings led the authors to make a tentative conclusion that CFS may be associated with a degree of personality pathology. A slightly larger sample was investigated in the study by Blakely et al. (1991) in which the MMPI was administered to 58 CFS patients and two control groups (one composed of chronic pain patients). Results revealed profile similarities between the CFS and chronic pain patients (in terms of physical and psychological symptoms) although the MMPI also revealed that the CFS patients manifested more deviant personality traits. This was interpreted from the *Hypochondriasis/ Schizophrenia* elevation that characterized the profiles of 14% of the patients; the authors speculated that this pattern might represent a possible risk factor for the development of CFS. Although similar profiles were found in 40% of the chronic pain controls, a more serious limitation is articulated by Abbey (1993) who questions the relevance of studies such as these by suggesting that the diagnosis of personality pathology in CFS could be spurious given the high incidence of depressive symptomatology in CFS patients, and the finding that personality pathologies are often resolved or lessened following treatment of the mood disorder.

More recently, Pepper et al. (1994) sought to find personality and psychological profiles that might differentiate CFS patients from two groups of fatigued controls (i.e. patients with major depression and multiple sclerosis). They found that while CFS patients manifested greater depression than the MS patients, the CFS patients showed significantly fewer personality

disorders and lower levels of depressive symptoms than did the depressed control group (see Table 2.1 for details). Following a more qualitative personality assessment of approximately 100 CFS patients, Surawy, Hackmann, Hawton, and Sharpe (1995) suggest that the premorbid personality of individuals with CFS is characterized by "marked achievement orientation, perfectionism, and high standards for work performance, responsibility and personal conduct" (p. 537). They also describe a tendency on the part their patients to repress emotion, "put on a brave face", and be overly concerned with what others think of them. They suggest that this particular personality constellation could act as a catalyst in the development and perpetuation of CFS.

2.1.1 CFS and Depression:

The findings of the various studies presented in Table 2-1 leave little doubt that depression is an important component of CFS; however, despite ongoing research, the precise relationship between CFS and depression remains unclear. Abbey and Garfinkel (1991) suggest that three possibilities exist in this regard: (1) depression is the cause of CFS; (2) depression is the result of CFS; and (3) CFS and depression are covariates. Each possibility is briefly explored below:

(1) *Depression as the Cause of CFS:*

Arguments that CFS is really just a manifestation of depression are fuelled not only by the high incidence of depression in CFS patients, but also the continued failure of research to isolate a specific viral or infectious cause for CFS. Komaroff (1993) suggests that depression is the most common cause of fatigue in patients who seek medical care for fatigue, with studies suggesting its coexistence in 16.7% to 73% of chronically fatigued patients (Gold et al., 1990; Millon et al., 1989). Some parallels between CFS and depression are certainly apparent; epidemiological studies reviewed by Abbey and Garfinkel (1991) reveal depression to be more prevalent in women as opposed to men (15-20% versus 8-10%). The age of peak onset is also similar to CFS at 25-44 years (ibid). Like CFS, a variety of somatic and cognitive complaints are apparent in depressed individuals. Somatic (vegetative) features include not only fatigue but also psychomotor retardation (70% of patients) and sleep disturbance (65%). Cognitive features of depression include impaired concentration (86%), memory problems, slowed information

processing, decision-making difficulties and slowed reaction time (Abbey & Garfinkel, 1991; Cohen, Weingartner, Smallberg, Pickar, & Murphy, 1982; Hamilton, 1992; Mathew, Largen, & Claghorn, 1991; Weckowicz et al., 1978).

Much of the argument as to why CFS is not a manifestation of depression revolves around claims that the nature of the apparent depression in CFS patients is qualitatively different from that experienced by more severely depressed patients. For example, Bell (1994) suggests that depression is generally not precipitated by a "flu-like illness"and that the diagnostic criteria for depression (DSM-III-R) do not include low-grade fevers, joint pain, swollen lymph glands and a range of other symptoms commonly reported by CFS patients. Subtle differences in the experience of concentration deficit are also evident; in depression, a positive correlation exists between extent of deficit and depth of depression, whereas in CFS, the impairment appears to be associated more with the timing and severity of fatigue (Jenkins, 1991). Differences in the nature of depression (e.g. reduced severity) between CFS patients and those with primary depression has been noted (Hickie et al., 1990) and there are indications that CFS-related depression parallels more closely the symptoms seen in patients with primary medical disorders (Blakely et al., 1991; Murray, 1992). It has been suggested that depressed CFS patients are less likely to report guilt and low self-esteem than patients with primary depression (Ray, 1991b). Wessely and Powell (1989) found a strong association between existing mood disorders (i.e. depression) and the onset of CFS, but felt that CFS was too heterogenous a condition to accept depression as the cause of CFS.

(2) *depression as a result of CFS*:

The argument for depression being a consequence of CFS comes from studies that show that depression can arise in response to protracted recovery patterns from illness.[22] Both Sharpe et al. (1991) and Ray (1991a) suggest that the loss of function and general malaise associated with CFS could easily give rise to symptoms of depression. In a related vein, it is generally accepted that a lack of exercise and avoidance of activity (as might be expected in a chronically fatigued

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Abbey and Garfinkel (1991) suggest that this phenomenon is best understood as a type of adjustment disorder (i.e. as a psychological response to a disabling illness).

individual) can produce detrimental effects on physical and mental well-being (Ornstein & Sobel, 1986). The problem with this argument is that psychological difficulties are apparent in the premorbid histories of some CFS patients (Kruesi et al., 1989; Taerk et al., 1987; Wessely & Powell, 1989) and so it could be argued that premorbid factors play a contributory role in the later manifestation of depression in some patients. On the other hand, the process of establishing cause and effect when making a retrospective diagnosis, can be problematic (Ray, 1991b).

Arguments against depression being the cause of CFS have generally attempted to prove that depression arises as a consequence of CFS (i.e. that CFS precipitates depression in affected individuals). Support for this contention comes from evidence that many viruses (including those implicated in the development of CFS) have been known to produce psychiatric symptoms (Lishman, 1987). The exact mechanism through which viral infection may cause depression is not fully understood, but is thought to involve immune system activation and the presence of circulating cytokines (e.g. interleukin and interferon). In this regard, Denicoff et al. (1987) have shown that the therapeutic use of cytokines produces symptoms of fatigue and depression. An early study attempting to investigate the relationship between viral infection and depression is one by Amsterdam et al. (1987). They were interested in assessing the relationship between depression and unrecognised chronic EBV infection; antibodies to EBV infection were studied in 43 patients diagnosed with major depression and compared with 46 age- and sex-matched healthy volunteers. These researchers reached two conclusions on the basis of their results: firstly, that depression was not associated with a deficit in cellular immunity sufficient to precipitate EBV reactivation; and secondly that there was no evidence to suggest that depression resulted from chronic unrecognised EBV infection. More recently, McAllister et al. (1992) found that progressive immune system dysfunction in HIV-infected individuals was associated with increased levels of depression and anxiety.

(3) *CFS and depression as covariates:*

The idea that CFS and depression are manifestations of some currently unknown underlying process or infection, is another possibility proposed by Abbey and Garfinkel (1991). They suggest that because some viruses are neurotropic, it is possible that viral infection could

cause affective changes (such as the onset of depression) through activation of particular brain circuits and receptor sites. Ray (1991a) argues that "while there may be an association between the two syndromes, this in itself cannot justify an assertion that one has etiological primacy" (p. 2). Nevertheless, it could be that the association between CFS and depression is related to a common pathway/factor which might be implicated in the pathogenesis of both (e.g. disordered immunity). This common pathway hypothesis has received some support from investigators who implicate the hypothalamic-pituitary-adrenal (HPA) axis as the mediator of depression and CFS symptomatology (See Chapter 3).

The complexity of the association between physical illness and depression makes it difficult for researchers to disentangle the relative effects of one condition on the other. Despite employing medical controls in their attempt to study depression in individuals with CFS, Blakely et al. (1991) were unable to establish causality.

What conclusions can be reached about relationship between depression and CFS? The limitations of current diagnostic instruments and procedures are highlighted by Ray (1991a) who suggests that the depression experienced by CFS patients may be more appropriately conceptualised as demoralisation or despondency in the face of an illness that may be prolonged, debilitating and of uncertain etiology. However, doctors may respond to this despondency with a tendency to over-pathologize or diagnose symptoms of depression in CFS patients. The other side of the coin is represented by cases in which CFS symptoms have been explained on the basis of masked depression. In this context, Sharpe et al. (1991) report an interesting case study in which a 17-year old schoolgirl with a missed diagnosis of bipolar depression made an almost instant recovery from apparent CFS symptomatology following administration of antidepressant medication. There are problems interpreting cases such as these, especially when one considers that CFS symptoms may share a common biological pathway with depression (i.e. the action of anti-depressant medication may be non-specific). Ray (1991b) believes that a major limitation in trying to understand the relationship between depression and CFS is that neither is a clear-cut condition and that the heterogeneity in symptomatology (with a high degree of overlap between the two conditions) makes it difficult to understand their causal association using current conceptual frameworks.

2.2 ABNORMAL ILLNESS BEHAVIOUR, CFS, AND PSYCHONEUROIMMUNOLOGY

The concept of abnormal illness behaviour was first introduced by Pilowsky in 1969 in an attempt to provide a framework for understanding functional conditions such as hysteria, hypochondriasis, chronic pain and conversion disorders (Pilowsky,1990). It has received subsequent elaboration by authors such as Mechanic (1986). Schweitzer et al. (1994) define abnormal illness behaviour as "the persistence in inappropriately perceiving, evaluating and acting in relation to one's health (i.e. a discrepancy between the appropriate sick role and the patient's behaviour in relation to their illness)" (p. 41). This definition derives from the observation that illness can be used as a vehicle through which an individual can express various personal and interpersonal problems, and that adoption of the sick role has some secondary gain for these individuals. Pilowsky (1990) distinguishes between those illness behaviours that are somatically focussed (e.g. Munchausen's syndrome) and those that are psychologically focussed (e.g. Ganser syndrome); an additional breakdown is made in terms of illness-affirming versus illness-denying symptoms.[23] Marked intra- and inter-variability is thought to exist in the expression of illness behaviour and determinants include not only sociocultural influences (such as prevailing norms)[24] but also personal predispositions which might include processes of introspection and self-evaluation (Mechanic, 1986). Careful assessment of the individual components making up illness behaviour (i.e. somatic, emotional, behavioural and sociocultural) is considered to be the first step in making a diagnosis (Pilowsky, 1990). The Illness Behaviour Questionaire (IBQ) appears to be a valid and convenient method of sampling such symptom dimensions (Pilowsky & Spence, 1983).

Hypochondriasis is thought to be an important expression of abnormal illness behaviour. Barsky and Klerman (1983) suggest that hypochondriasis may be understood as a perceptual amplification of bodily sensations and their cognitive misinterpretation, or as a socially learned

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As a detailed breakdown of the components making up Pilowsky's diagnostic categories is considered to lie beyond the scope of this dissertation, the interested reader is referred to Pilowsky (1990) for further elaboration.

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Pilowsky (1990) suggests that the ultimate indicator of societal recognition of an "illness", is acceptance of its compensable value in a court of law.

illness.[25] Both have relevance for CFS. Woods and Goldberg (1991) consider CFS symptoms such as irritability, exhaustion, and lack of energy, to be closely associated with depression and anxiety, but because of their inconsistency and reduced severity, can be considered as borderline symptoms in terms of *caseness*. They further suggest that with increased severity, the CFS symptoms may meet the diagnostic criteria for depression, anxiety and other psychiatric disorders - a process referred to as *destabilisation*. The process of destabilisation is determined by multiple factors which include: life stress, previous episodes of depression and lowered immune response.

Following evidence of the protracted recovery of some CFS patients, investigators have attempted to identify some of the variables that might potentially influence morbidity. Woods and Goldberg (1991) comment that patients who accept some responsibility for their symptoms are more likely to believe they can contribute to their own recovery. Likewise, it has been demonstrated that those who attribute their illness to some external event (e.g. virus) tend to have a protracted recovery. However, there is a shortage of data on what constitutes adaptive as opposed to maladaptive ways of coping in CFS patients. One recent study (Ray, 1992) devised an unpublished illness management questionnaire which was subsequently administered to 207 patients. A principal components analysis of the questionnaire items identified four factors: maintaining activity; accommodating to the illness; preoccupation with symptoms; and information-seeking. These factors were found to be significantly related to measures of depression and anxiety. The possibility that individuals with CFS may have a tendency to over-attribute their psychological difficulties to somatic causes has already been mentioned in this literature review. Recently, Howlett and Lindegger (1996) investigated attributional style in a local sample of CFS patients ($n = 41$) and compared their responses on the Zung Self-Rating Scale for Depression, Attributional Style Questionnaire (ASQ), and IBQ, to control groups of depressed and chronically physically ill patients. Results revealed that CFS patients were more similar to depressives on measures of depression and illness behaviour, but more like chronically

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Although the incidence of CFS in Zulu-speakers is currently unknown, personal communication with local CFS experts suggests that it is a rare (but not unknown) occurrence. Although there may be multiple reasons for this Pilowsky (1990) offers an interesting explanation by suggesting that traditional healers do not make a diagnosis, but rather suggest that the symptoms have significance in terms of offended ancestral spirits. In such a situation, Pilowsky claims that "hypochondriasis or abnormal illness behaviour cannot arise, since the syndromes are dependent upon the existence of a healing profession that claims and is granted special authority by a society and offers the benefits of its own knowledge and treatments" (p. 209).

physically ill patients on attributional style. This finding was interpreted as evidence of a distinctive illness behaviour in CFS patients characterized by high levels of disease conviction and somatization. In another local study, Weinberg, Louw, and Schlomer (1994) investigated the self concept of 50 CFS patients using a repertory grid technique. Results indicated that the phenomenon of contracting CFS exerted a detrimental effect on self concept that remained independent of medical confirmation of the illness. In addition, the respondents endorsed what they perceived to be a largely negative public conceptualization of CFS (the authors postulated that such findings could lead to symptom exacerbation and protracted outcome).

Schweitzer et al. (1994) attempted to replicate the Hickie et al. (1990) study (see Table 2-1). A similar degree of psychiatric comorbidity was found although in contrast to the Hickie et al. study, a higher degree of general hypochondriasis was indicated by the IBQ. Taking their comparison one step further, Schweitzer and colleagues contrasted their subject's scores with the reported norms of hypochondriacal, psychiatric and malignant disease patient group, and found that there was no significant difference between their sample and hypochondriacal patients. At the same however, they acknowledged that this finding could not exclude an organic basis to the symptoms and argued that their findings could signify poor psychological adjustment to organic or bodily symptoms.

An interest in assessing the role of various factors on the severity of illness burden (i.e. lifestyle disturbance) led Antoni et al. (1994) to investigate physical symptoms, cognitive appraisals, and coping strategies in two subsets of CFS patients (n = 26 with concurrent depression, n =39 without). The Sickness Impact Profile (a measure of the perceived extent to which an illness may have compromised an individual's lifestyle) was administered to both groups.[26] Multiple regression analysis of the results suggested that the way in which CFS patients perceive and cope with daily demands, may contribute to ongoing symptomatology. Specifically, it was found that the greatest physical and psychosocial disturbances were evident in those patients who reported more maladaptive cognitive appraisal and more frequent use of

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Additional psychosocial measures (used in computing a predictor model) included the life orientation test (LOT), the dysfunctional attitude scale (DAS), the automatic thoughts questionnaire-revised (ATQ-R), and a 57-item measure of cognitive and behavioural coping strategies (COPE).

disengagement/denial coping strategies. The authors speculated that compromised social relationships would in turn lead to social alienation and subsequent symptom amplification.

To summarize, a commonly held viewpoint is that CFS symptoms are perpetuated by disease conviction and by maladaptive beliefs about improvement possibilities; these are considered to be abnormal illness behaviours. There is also some evidence that personality factors (including attitudes, beliefs and thoughts) can perpetuate disability as well as exacerbate disability in many chronic conditions. One simple but useful hypothetical model linking these various factors has been proposed by Sharpe (1993) and is summarized in Figure 2-1. Sharpe notes that CFS symptoms may be precipitated by infection or severe life stress. In this model, maladaptive cognitions and abnormal illness behaviour may lead to symptom exacerbation and depression (attributional style may be also lead to symptom exacerbation). Resulting inactivity may lead to further negative cognitions and physiological changes that result in symptoms of fatigue, impaired concentration and myalgia. Sharpe also notes that social influences may reinforce these cognitions. The end result is a vicious circle of symptoms that may be self-perpetuating. Because of the importance of cognitive and behavioural aspects of this vicious-circle scenario, Sharpe advocates treatment that will specifically modify these parameters.

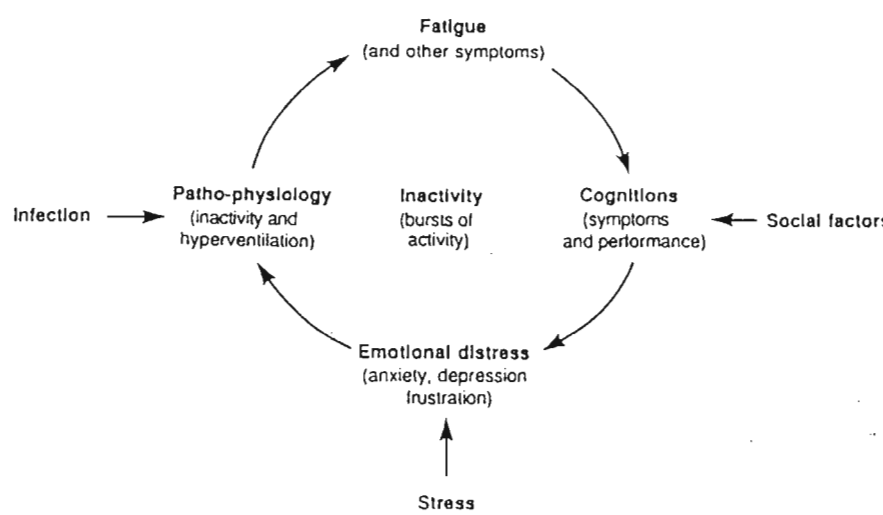

Figure 2-1. Hypothetic Model of CFS Perpetuation (reproduced from Sharpe, 1993, p. 302).

2.2.1 Psychoneuroimmunology:

Consideration of the issues outlined thus far leads us directly into the field of psychoneuroimmunology. While the biological aspects of this complex interactive system are reviewed more thoroughly in the next chapter, some reference to the psychological variables is made in this section.

It has long been known that psychological stress predisposes an individual to infection; alterations in the levels of various antibodies are thought to be the mechanism through which this occurs (Dorian & Garfinkel, 1987). Representative examples of altered immunity in response to a variety of stressors include findings of reduced IgA concentrations in students at exam time (Kiecolt-Glaser et al., 1987) and a high risk of EBV infection in military students who came from families with high expectations of their success (Kasl, Evans, & Niederman, 1979). In a review of research in this area, Hotopf and Wessely (1994) conclude that even comparatively minor stresses are associated with changes in immune function and susceptibility to infection. Recent studies have revealed that susceptibility to upper respiratory tract infection (URTI) is positively linked to psychological stress (Cohen, 1995) and is moderated by psychosocial resources such as social support and family structure (Turner-Cobb & Steptoe, 1996). In the Cohen study, negative emotions were found to predict not only susceptibility but also severity of illness. Bruce-Jones, White, Thomas, and Clare (1994) report that recurrent herpes virus infections (oral and genital types) are associated with stress, while research has also shown that traumatic events such as childhood separation can exert detrimental effects on *later* immune system functioning (David, 1991b; Taerk & Gnam, 1994;). Ballieux (1994) suggests that the perception of a stressor is a crucial mediator of the body's immunoregulatory function/ dysfunction. In this respect, Levy et al. (1990) found that natural kill cell activity in breast cancer patients was associated with perceived quality of emotional support. Other studies have documented the negative impact of stressors such as bereavement, job stress, unemployment and marital problems on immune system functioning (Hayes, 1995).

The importance of acknowledging stress within a wider biological framework is emphasised by Cohen (1995); he suggests that persons exposed to psychological stress often

engage in poor health practices (e.g. smoking, inadequate diet and exercise regimes, and poor sleeping habits) which may exert additional immunosuppressive effects. Empirical support for this viewpoint comes from a study on HIV-infected individuals in which it was found that aerobic exercise programs and cognitive behaviour therapy led to decreased antibody titres for EBV and HHV-6 (Esterling et al., 1992). Recently, it has been suggested that alcohol is detrimental to immune system functioning in HIV-infected individuals (Bornstein, personal communication, April 1996); in this regard it is interesting to note that CFS patients often develop an aversion to alcohol, possibly as a self-protective mechanism to enhance the integrity of the immune system. However, the idea that alcohol has immunosuppressant properties was not supported in a study by Turner-Cobb and Steptoe (1996); they found that of 55 families, regular drinkers were less likely to experience URTI than non-drinkers, whereas smoking, exercise and sleep were not associated with increased risk of infectious illness. Further well-controlled, longitudinal studies in this area may provide some clarity with respect to the role of alcohol and other risk factors in CFS.

In comparison to the research on stress and immunity, the relationship between immune dysfunction and psychiatric disorder is less well understood. Nevertheless, it is established that immune dysfunction is found in depressed patients and that this appears to be associated with hypothalamic-pituitary-adrenal (HPA) axis overactivity (David, 1991; Schleifer et al. 1984). Both Dorian and Garfinkel (1987) and Hotopf and Wessely (1994) emphasize that such overactivity may be determined by multiple factors. For example, the HPA axis is sensitive to a range of environmental factors although the precise interaction between these factors, depression, immunity and chronic fatigue is still unclear. Other psychiatric conditions that have been studied with reference to immune system dysfunction, include anorexia nervosa and schizophrenia.[27]

In a pre- and post-test placebo-controlled study specifically devised to investigate the relationship between immunological status and psychological status of CFS patients, Hickie et al. (1992) found that only those patients who received immunotherapy revealed a consistent correlation between improved depression and cell-mediated immunity (i.e. providing support to

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the reader is referred to Dorian and Garfinkel (1987) for a review of studies on these conditions.

the view that depressive symptoms occur secondary to immunological dysfunction). Further complexity is apparent in the possibility that the response of the immune system to virally-induced stress is probably genetically determined (Goldstein, 1993); this hypothesis might explain why not all people exposed to the same virus develops CFS.

The idea that psychological factors can influence immunity and disease susceptibility is very much a topical issue within the current CFS literature. Links between the immune system and psychological factors are thought to be bidirectional (see Chapter 3), thus a pathway exists for the influence of the immune system on affect and cognition. If, as is currently hypothesised, the immune system is triggered by viral infection, then symptoms such as fatigue, malaise, and depression could be easily understood as consequential to this activation, and could act to perpetuate disordered immunity (Ray, 1991b).

2.2.2 Psychosocial Factors and CFS

The role of psychosocial factors in illness behaviour and CFS has been the focus of some recent research. In particular, there are clear indications that social environment is an important determinant of illness behaviour and susceptibility to illness (Abbey, 1993; Kiecolt-Glaser & Glaser, 1995; Ornstein & Sobel, 1987). Increased immune competence has been associated with supportive social networks and feelings of belonging (Adler & Mathews, 1994), while patient expectations and belief systems have also been mentioned as important mediators of illness (Sharpe, 1991; Woods & Goldberg, 1991). According to Hotopf and Wessely (1994), data on the effect of personality factors on illness behaviour has been under-researched.

Ware (1993) stresses the importance of identifying CFS sufferers' *local social worlds* (i.e. interpersonal experiences that occur in the family, community, and workplace) as a modulator of illness behaviour. The hard-driving lifestyles of some CFS patients has already been referred to in Chapter 1. Ware suggests that the interpretation or meaning of these feelings of being overwhelmed by lifestyle demands (i.e. stress) is best conceptualised in a biopsychosocial framework. According to Ware, CFS occurs in some individuals following an over-subscription

to social norms that "dictate exhaustion as a way of life" (p. 66). Ware's research indicated that the outcome was not always considered to be unfavourable by CFS patients; in fact, she found that 44% of her study participants perceived CFS as a positive catalyst for lifestyle change. In connecting this experience to a larger social framework, Ware believes that social processes play a role in CFS development and course; she states that:

> attributions of cause to social sources, the symbolic representation of social experience in the core complaint of fatigue, reports of an illness-induced change in lifestyle suggestive of a rejection of cultural norms - all of these factors connect CFS to local worlds and the large social forces they mediate (p. 68).

That stress is implicated in the development of CFS, has been alluded to by a number of authors. For example, Stricklin et al. (1990) report that CFS sufferers experienced more loss-related life events in the 12 months prior to CFS onset than healthy controls. Ware (1993) also found that almost half of her sample ($n = 40$) cited stress as a contributing or precipitating factor in CFS onset. In a questionnaire survey of 110 UK patients with CFS, Benton and McLellan (1993) found a high level of current psychosocial distress (e.g. loss of self-esteem, social isolation, interpersonal dissociation and a lack of communication confidence). This distress was further increased by a perceived lack of social support systems. Vercoulen et al. (1994) used the Sickness Impact Profile (SIP) to assess psychosocial problems in 298 CFS patients; they found that 27% of patients reported difficulties in social relations, while 29% reported not being satisfied with current social interactions.

The influence of social adversity on recovery from glandular fever (EBV infection) was examined in a prospective study of 250 patients by Bruce-Jones et al. (1994). Classifying subjects on the basis of their own fatigue syndrome criteria, three 6-month outcome categories were described: (1) those who were considered to be well; (2) those who developed a fatigue syndrome; and (3) those who fulfilled the criteria for a psychiatric diagnosis. Results indicated that while there were no associations between significant stressors and psychiatric morbidity at the onset of infection, a positive association developed at 2.5 months after onset. In particular, the authors noted that social adversity was significantly associated with depression. In contrast,

social adversity was not significantly associated with the development of a post-infectious fatigue syndrome or delayed physical recovery for the first six months following onset. Thereafter, they agree that social adversity could act to maintain the condition.

Using a range of questionnaires and rating scales, Lewis et al. (1994) examined a range of psychosocial factors (e.g. life events, Type A behaviour, coping strategies and social support etc.) to see which might be associated with CFS onset in 47 patients who fulfilled the Oxford criteria. These patients were compared to 47 irritable bowel syndrome patients (IBS) and 30 healthy controls. Although there were no group differences for life events, both the CFS and IBS groups rated themselves as more "hard driving" prior to illness than the control group. Interestingly, and in contrast to popular conceptions of CFS and research by Woods and Goldberg (1991), it was found that the global Type A behaviour pattern was not a relevant construct in characterising CFS sufferers. In fact, the CFS group rated themselves as better listeners (a Type B characteristic) than the control groups. This is consistent with Ware's (1993) finding that CFS sufferers tend to be highly involved in doing things for others. Other findings that emerged from this study included findings of inadequate coping strategies and low perceived social support in the CFS group. The authors suggested that this latter finding could increase vulnerability to CFS through the mechanism of emotionally induced effects on the neuroendocrine and immune system. Such a conclusion would be compatible with existing research showing that stress prolongs recovery from physical illness (Ornstein & Sobel, 1987) and that social isolation is a major risk factor for disease (Hayes, 1995). A further study investigating the relationship between fatigue, psychiatric morbidity and social stress was made by McDonald, David, et al. (1993). Results of a correlation matrix indicated that CFS sufferers with high levels of psychiatric morbidity, also had higher levels of fatigue and lower levels of social support and satisfaction.

Finally, in acknowledging the notion of psychological and physical vulnerability in CFS patients, Taerk and Gnam (1994) propose a model emphasizing the role of faulty object relations in the pathogenesis of CFS symptoms. In their model, vulnerability is thought to originate from a diminished capacity to regulate internal states and failed responses to certain types of stressors (i.e. disturbances in object relations). In an illustrative case study, the authors reported how the onset of CFS symptoms in one particular patient followed the death of the patient's brother. In

their conceptualization of this case, the brother had served as an important idealized self-object which had helped the patient to overcome self defects that originated from early child-caregiver misattunement. His death caused a dysregulation of psychological and physical systems leading to the onset of CFS. In this kind of psychodynamic model, relationships with compensatory (idealised) others are important in maintaining the regulatory mechanisms that prevent psychological and physiological collapse.

2.3 CONCLUSION

Having considered some of the psychological aspects of CFS in this chapter, there can be little doubt that to attempt to conceptualise CFS purely in terms of discrete organic or psychological factors is problematic if one views these as mutually exclusive explanations. On the basis of the studies reviewed here, it is clear that CFS is a heterogeneous condition comprised of multiple psychological and organic factors; to attempt to separate these out for individual study is a difficult task. It has been argued (Bell, 1994) that CFS is clearly an organic condition in that its symptomatology does not fit established psychiatric diagnostic categories. On the other hand, there is clear evidence of a high degree of psychiatric morbidity in the histories of some CFS patients. The most useful way of understanding CFS is to acknowledge both biological and psychological dimensions; in this respect, CFS is best viewed as a heterogeneous and multidimensional condition, involving interaction between somatic symptoms and immunological responses on the one hand, and psychological antecedents and consequences on the other.

It is difficult to know how to interpret the findings of the psychosocial aspects of CFS. On the basis of the studies reviewed in this chapter, one gains the impression that CFS cannot be fully understood without reference to the psychological and psychosocial factors that influence its development, manifestation and course. Viewed within the context of abnormal illness behaviour and psychoneuroimmunology, one is almost overwhelmed by the complexity of the interplay between biological, psychological and social factors. Hopefully, continued research (that takes cognizance of this multidimensional framework) will allow for increasing disentanglement and understanding of this complex condition.

CHAPTER 3

THE NEUROBIOLOGY OF CFS

It should be evident from previous chapters of this literature review that CFS is a disease entity of unusual complexity. Having reviewed issues related to case definition, clinical presentation and psychopathology, the next focus of the literature review is to consider the neurobiological aspects of CFS. Despite the failure to identify any consistent biological markers up until the present time, the idea that the symptoms underlying CFS can be explained in biological terms still occupies a prominent position in the CFS literature. Indeed, Schulte (1991) comments that CFS "is a disease in search of laboratory confirmation" (p. 87). Biological markers (which could be molecular, biochemical, morphological, cytologic or physiological in nature) have obvious potential value in informing the nature, course and treatment of CFS. Moreover, as has been pointed out by Polich, Moore, & Wiederhold (1995), an objective test for CFS has some advantage over subjective self-reports (in terms of diagnostic accuracy).

This chapter examines a number of issues related to the neurobiology of CFS. It begins with a brief review of the effects of viral conditions on CNS function and while the neuropsychological sequelae following viral infection are covered in this section, the specific neuropsychological correlates of CFS are held over for presentation in Chapter 4. This is followed by a brief presentation of the various specialized investigative techniques and representative findings. Next, are sections on the pathophysiology of fatigue, the association between CFS and immune system functioning, and an examination of the neuroendocrine and neurotransmitter correlates of CFS. Reference to the field of psychoneuroimmunology (i.e. the system of interactions between behaviour, the brain and the immune system) concludes the chapter and an attempt is made to evaluate the biological basis of CFS within this framework. While some apology is offered for the fragmented nature of this chapter, it would be fair to say that this reflects the diversity of methodologies and theoretical frames of reference that guides neurobiological research.

3.1 CNS EFFECTS OF VIRAL INFECTION

The effects of viral infections on brain function are well documented in standard texts of neuropsychology and neuropsychiatry (e.g. Lishman, 1987; Reitan & Wolfson, 1985). A commonly cited example of viral disease causing neuropsychological deficit, is the influenza epidemic of 1918 which produced encephalitis *lethargica* and psychosis in some of its victims. More recently, the literature has noted that HIV infection exerts its initial effect on the CNS, while the recent (1996) UK outbreak of Creutzfeldt-Jakob disease in a few individuals (due to a so-called slow-virus) received extensive media coverage throughout the world.

In conjunction with the recognition that CFS symptomatology may arise subsequent to viral infection, there has been some interest in assessing the possible effects of such infection on nervous system functioning. Under normal circumstances the brain is well protected from viral and other infections (Reitan & Wolfson, 1985). Part of this protection is offered by the blood-brain barrier which restricts the entry of adverse substances and pathogens. However, the anti-body production capacity of the nervous system is not as efficient as that elsewhere in the body so that if an infection manages to take hold, it can develop into a serious condition that may be difficult to treat. The problem is compounded by the nature of the cerebrospinal fluid which is an ideal culture medium (ibid). The consequence of this vulnerability is the relative ease with which viruses can replicate in the brain tissue as well as the capacity to persist in the nervous system for long periods of time (Webb & Parsons, 1991). There is some debate about whether viral infections of the nervous system are caused by direct invasion from outside the body, or whether they result from an auto-immune reaction from viruses already in the body. For example, Lishman (1987) reports that between 80-90% of healthy adults have detectable herpes simplex antibodies, yet only a relatively small percentage of persons will actually develop herpes simplex encephalitis. As with other forms of infection, a weakened immune system can predispose an individual to opportunistic infection (Wessely, 1993).

Viral infection of the brain results in two distinct syndromes. The first of these, *aseptic meningitis*, refers to inflammation of the meninges and can result from infection from a wide variety of benign viruses (Reitan & Wolfson, 1985). The second is *encephalitis*, a term reserved for viral infection of the brain substance itself (Lishman, 1987). Although the clinical features

of acute encephalitis is well recognized,[28] there appears to be less conclusivity about the nature of the transient cerebral change associated with the more benign viruses. These would include common viruses such as measles, mumps, herpes simplex, and the group of viruses implicated in the onset of some cases of CFS (e.g. influenza, herpes zoster, varicella, Coxsackie B, infectious mononucleosis, poliomyelitis, and ECHO viruses). The prototypical infective process is described by Reitan and Wolfson (1985):

> The onset may be sudden or gradual; there is moderate elevation of temperature, headache, stiff neck, vomiting, and a general feeling of illness which usually lasts about 10 days. Full recovery usually occurs within a period of a few days to a few weeks, although some patients complain of fatigue and malaise for a few months after the illness (p. 231).

Considerable variations of this clinical picture may exist, with some viral agents causing mild or even subclinical infections. Furthermore, individual variation may be apparent (Reitan & Wolfson, 1985). These are important points for the consideration of a viral substrate to CFS, since they allow for the possibility that disruption of brain function may be subtle. Brain function may be disrupted in various ways. For example, infection may alter the functioning of neural cell membranes and cause impaired neural transmission; alternatively, it may interfere with the basic metabolic processes of the neural cell (Kolb & Wishaw, 1990). Focal demylenization and diminished blood flow associated with vascular changes have also been noted (Schwartz et al., 1994a). Typically, the neuropsychological effects of brain infection tend to be widespread, reflecting diffuse brain involvement (Lezak, 1995). However, specific memory deficits involving the axial or midline brain structures and brainstem are commonly seen (Lishman, 1987; Moriarty, 1996; Schwartz et al., 1994b). Localization of viral invasion to areas of the brain associated with mood, drive, sleep, and the control of energy (i.e. hypothalamus, limbic system and brain stem) is specifically mentioned by Webb and Parsons (1991) and Costa et al. (1995).[29] Moreover, viral

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The most prominent symptoms include confusion, coma, convulsions, delirium, headaches, language disturbance and cognitive or intellectual deterioration (Magner et al., 1986)

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Neuropathological work on animals has revealed a predilection of the herpes simplex virus for the brainstem and diencephalon.

invasion of these brain regions will affect associated neurotransmitter systems (especially those of the HPA axis). The CNS effects of some of the more common viral infections are outlined below:

(1) *Infectious mononucleosis (EBV):*

The principal neurologic manifestation of this illness is a mild fever, sore throat, and involvement of the lymph glands. Reitan and Wolfson (1985) maintain that only about 5% of cases show central nervous system involvement and that the symptoms are usually mild. A more detailed review of EBV encephalopathy is provided by Grafman, Johnson, and Scheffers (1991); they suggest that the prevalence of neurologic disease in patients with infectious mononucleosis ranges from 0.7% to 5.5%. Reported symptoms include intellectual and memory impairment, hemianopia, hemiparesis, aphasia, and abnormal EEG findings. An interesting (albeit atypical) case is reported by Leavell, Ray, Ferry, and Minnich (1986). The patient presented with left hemiplegia following EBV infection; she was discharged following rapid improvement but readmitted five days later with confusion, ataxia, fatigue and hallucinations. She was also disoriented and displayed sexually inappropriate behaviour. An EEG taken at this time was slow and bilaterally disorganized. The symptoms had resolved completely at a three-month follow-up, although Grafman et al. (1991) suggest that mild symptoms have been known to persist in other cases.

(2) *Coxsackie viral infections:*

Two types are recognized, type A and type B, and they occur predominantly in children. Both are known to give rise to aseptic meningitis that can bear some resemblance to poliomyelitis (i.e. a predilection for the muscle and nervous tissue is suggested).

(3) *ECHO viruses:*

Over 40 types have been identified. The clinical manifestations commonly consist of a febrile illness, diarrhea, and upper respiratory tract infection (URTI). When the CNS is involved, the clinical picture is one of aseptic meningitis, although some predilection for the brainstem and cerebellum has been noted, giving rise to cerebellar signs and ataxia (Reitan & Wolfson, 1985).

(4) *Measles encephalitis:*

Although regarded as a rare complication of measles, CNS involvement manifests itself as fever, headache, and specific neurological signs. The subclinical picture has been poorly studied, although Reitan and Wolfson report that approximately 50% of people with measles encephalitis demonstrate EEG abnormalities. Griffin (1991) notes that immunologic abnormalities may persist for weeks after the measles virus has been cleared.

(5) *Mumps virus:*

Mumps is primarily an infection of the salivary glands, although subclinical CNS involvement is common. An aseptic meningitis characterized by headache, stiff neck and confusion may occur in more severe cases.

(6) *Polioencephalitis:*

Initial symptoms of poliovirus infection include headache, neck pain, low grade fever and myalgia which may be accompanied by paresis. Hypersomnolence and EEG slowing have also been documented and imply an encephalitic process principally affecting brainstem regions (Bruno, Frick, Creange, Zimmerman, & Lewis, 1996). These symptoms share some features with CFS (see also Section 1.1.2 in Chapter 1) and have resulted in diagnostic uncertainty in past outbreaks; one difference is that recovery is generally less protracted in polioencephalitis. Mental and physical fatigue are commonly reported as components of the post-polio sequelae (PPS), and may result in a range of neuropsychological deficits especially involving attention and information processing (ibid). By virtue of its neurological and neuropsychological profile, Bruno and colleagues are of the opinion that poliovirus represents a prototype for a CFS-agent (in terms of decreased cortical activation and impaired attention). They have recently presented a theory (termed the *Brain Fatigue Generator*) to explain aspects of mental and physical fatigue in CFS.[30]

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[30] This theory stresses the importance of the basal ganglia (site of the *Brain Fatigue Generator*) in the monitoring and moderating of cortical and motor activation. The basal ganglia receive a high afferent input from the cortex, and send excitatory efferents to the descending reticular formation; in short, it is in a position to direct attention, perform motor behaviour and maintain wakefulness. Essentially, the idea behind this theory is that some (viral) agent acts to reduce cortical activation, which in turn causes a reduction in the firing rate of putamen neurons. The net effect of these changes is fatigue, expressed as impaired attention, feelings of exhaustion, reduced muscle tone, and a reduction in cortical activation.

(7) *HIV-1 encephalopathy:*

The human immunodeficiency virus type 1(HIV-1) causes an encephalopathy known as the AIDS dementia complex which is characterized by abnormalities in cognition, motor performance and behaviour. Neurocognitive symptoms include deficits in concentration, forgetfulness and slowed thought, while neuropsychological test results often give the impression of a subcortical dementia characterized by behavioural and mental slowing (Portegies & Goudsmit, 1991).

(8) *Persian Gulf Syndrome:*

This is a relatively new (and controversial) diagnostic label given to Gulf War veterans presenting with a range of cognitive and somatic complaints. Symptoms include fatigue, headache, abnormalities of heart rate and blood pressure, body temperature abnormalities, depression and memory loss (Goldstein, Beers, Morrow, Shemansky, & Steinhauer, 1996; Moriarty, 1996). The condition has been described as a brainstem encephalitis caused by exposure to toxins,[31] radiation, and multiple vaccinations, and is thought to be related to immune dysregulation involving interleukin-2 (IL-2). Baumzweiger maintains that the symptomatology implicates hypothalamic disturbance and is associated with the reactivation of latent retroviruses (e.g. EBV) in certain cases. Using a neuropsychological test battery known to be sensitive to neurotoxic conditions, Goldstein and colleagues failed to find evidence of significant impairment; however, an impairment index derived from 14 variables in their test battery found that the experimental group performed significantly worse than matched controls. Like CFS, the role of psychological stress has been cited as a variable in illness onset (Levine, 1996).

Neuropsychological dysfunction associated with the more benign viral infections is not well documented in the literature and there is a shortage of follow-up studies. Magner, Kirzinger, and Spector (1986) describe the case of a 23 year-old male with subsequently diagnosed viral encephalitis who showed no gross neurological abnormalities on presentation, but who manifested attentional and memory difficulties, the severity of which the authors considered to approximate a mild dementia. Neuropsychological evaluation using the Luria-Nebraska Neuropsychological Battery (LNNB) revealed widespread dysfunction with only motor skills and

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Quoting unspecified sources, Moriarty claims that "hundreds of tons of neurotoxins and bacterial toxins were forward positioned in the Gulf, on SCUD missiles and hand-held rocket launchers that were fired into Israel and Saudi Arabia" (p. 2).

receptive language ability remaining intact. At a three-month follow-up the neuropsychological profile was essentially normal with the exception of writing difficulty and residual memory impairment (these had been the most severely affected at the first evaluation). Intellectual assessment revealed a major deficit in the more fluid problem-solving skills which again had resolved on follow-up.

Howard and Lees (1987) describe four cases of apparent viral encephalitis, all with varying symptomatology. Three of the patients presented with a non-specific illness characterized by headache and general malaise suggestive of aseptic meningitis. Although no viral etiology could be established, the clinical symptoms were ascribed to the toxic effects of the virus, and diffuse cortical involvement was suggested by the authors. In addition, all had abnormal EEG's with pronounced slow wave activity.

In reviewing outcome studies of non-specific viral meningitis, Hotopf and Wessely (1994) note that neuropsychological sequelae can include decreased IQ, concentration difficulties, mental fatigue, neurasthenia, and headache. However, recovery is complete for the majority of individuals within 12 months from infection.

Transient neuropsychological deficits have been associated with the common cold and influenza (Smith, 1992; Smith et al., 1989). Drowsiness, confusion, and impaired judgement associated with influenza have been likened to an "influenzal encephalopathy", and can involve EEG changes that are epileptiform in nature (Smith, 1992). Likewise, colds have been linked to slowed reaction time and performance decrements in tasks of auditory and verbal perception in schoolchildren (ibid).

Researchers at the MRC Common Cold Unit in England (Smith et al., 1989, Smith, 1992) have conducted a number of investigations into the effects of colds and influenza on human performance. Following viral inoculation, performance deficits tended to be worse for those subjects who developed influenza, although the deficits were more prolonged in those subjects who developed colds. The authors noted that impairment continued even when subjects were symptom-free and concluded that the CNS effects of viral infection may be observed in the absence of clinical symptoms. A transfer effect was suggested as a possible explanation; i.e. that

volunteers perform a task in a certain way when they have a cold, and continue in the same way after they have recovered. This kind of effect is analogous to the literature on stress and performance that shows that subjects who have been performing badly in a noisy environment, continue at a similarly low level of performance when environmental conditions are quiet (Smith et al., 1989). One explanation offered by Smith and colleagues has focussed on the continuing effects of immunological changes following cessation of clinical symptoms. One of their studies investigated the question of whether the CNS deficits might be due to the presence of interferon alpha (this is a cytokine which represents the body's systemic response to viral infection). It was found that an injection of interferon alpha produced influenza-like symptoms in healthy volunteers as well as specific performance deficits similar to those seen in influenza virus infection. However, an exact match of the performance deficits was not found and the authors concluded that the causal relationship was relatively weak. Nevertheless, the notion that CNS effects may be caused by viral-induced immunological changes is also recognized by Lishman (1987). This finding has some relevance for CFS patients who have been found to have elevated levels of interferon (Mowbray &Yousef, 1991)

Subsequent studies at the Common Cold Unit suggested that common colds can give rise to a wide range of performance deficits which include less than optimal recall of complex (semantic) memory, decreased arousal, and susceptibility to visual illusion (Smith, 1992). In relating his own experiences of the neurocognitive deficits associated with CFS, a flight surgeon suggests that the diminished concentration, memory and calculation difficulties, slowed reaction time, and mild word-finding difficulty, are consistent with a chronic generalized encephalitis (Harvey, 1989).

Studies comparing the neurocognitive profiles of CFS patients with other types of viral infection have not yet appeared in the literature. However, a study by Smith et al. (as cited in Smith, 1992) compared 25 CFS patients with 32 healthy controls and 10 patients with a prolonged illness following influenza. Although the CFS subjects were slower than the influenza subjects on measures of psychomotor speed, the influenza subjects were found to be more impaired on attentional tasks (e.g. Stroop). Both groups manifested memory deficits relative to healthy controls. An extension of this study led Smith and colleagues to compare their CFS subjects with three AIDS patients; results indicated similar levels of performance between these two groups (as

cited in Smith 1992).

In summary and conclusion, relatively benign viral infections of the brain (such as those caused by colds, influenza and possibly CFS) can give rise to specific CNS effects; these include performance deficits across a range of neuropsychological tasks. Of importance in the study of CFS is the finding by Smith (1992) and others, that performance deficits following infection may continue after resolution of the clinical symptoms. The nature of persistence of these effects is not entirely clear from the literature; nevertheless, it is reasonable to suggest that if CFS is caused by a viral trigger or persistent viral infection leading to a benign form of encephalitis, then neuropsychological deficits should be demonstrable on testing. This assumption forms part of the rationale of the current investigation.

3.2 SPECIALIZED INVESTIGATIVE TECHNIQUES

Neurobiologists have at their disposal a wide range of investigative techniques which can be used to study CFS. This section reviews some of the methods which have appeared in the literature in the search for a biological basis to CFS.

3.2.1 Electrophysiology:

Despite the potentially useful application of electrophysiological methods in the study of CFS, relatively few studies have employed this paradigm. Two broad types of electrophysiological recordings can be identified: (1) electrocardiograms; and (2) electroencephalograms (including evoked potential studies). While a small number of studies have been carried out in the latter category, only one study has specifically investigated the electrocardiograms of CFS patients (Lerner, Lawrie, & Dworkin, 1993). In their study, a retrospective analysis of the 24 hour cardiac response of affected individuals was compared with a comparison group of 276 hospital patients. Subtle cardiac dysfunction in CFS patients was found and the authors raised the possibility that inefficient cardiac response in day to day activities could provide an etiological explanation for ongoing fatigue.

With regard to brain electrophysiology, it seems that the first report of the EEG correlates of CFS is a study by Pampiglione, Harris, & Kennedy (1978). They described the EEG features of 36 adults examined between 1960 and 1964 and 12 children examined between 1957 and 1977. All had received a diagnosis of myalgic encephalomyelitis. Results revealed mild abnormalities comprised of an excess of slow-wave activity and occasional appearance of sharp components. There was no obvious relationship between the severity of the EEG disturbance and clinical state; in addition, the authors remarked on the dissimilarity of their findings with those normally associated with viral infection. Unfortunately, evaluation of this study is limited by the lack of specific information about the results (e.g. frequencies of occurrence of the EEG abnormalities). The only other published EEG study found for inclusion in this literature review is one reported by Jamal and Miller (1991). Modest non-specific changes involving irregular slow wave activity were found in 80-85% of CFS patients, with the authors concluding that some

electrophysiological similarity existed between CFS patients and individuals with multiple sclerosis. As with the study by Pampiglione, the severity and extent of EEG changes appeared to be unrelated to the severity of the symptoms.

One unpublished local investigation of EEG changes associated with a reaction time paradigm has been conducted (Sargent, 1994). EEG power spectra were recorded from 10 CFS patients and compared with 8 healthy controls. There were no baseline differences in terms of median frequency or amplitude between the two groups, although differential patterns of hemispheric activation were found across task performance. Specifically, while healthy subjects showed increased activation of the left hemisphere with corresponding decreased activation in the right hemisphere, CFS patients showed the reversed pattern. These results were interpreted as providing evidence for lower basal arousal in the left hemisphere of the CFS group (a finding which would be consistent with some of the neurocognitive deficits reported by CFS sufferers, e.g. word-finding difficulties, verbal memory problems, computational difficulties etc.).

Cortical evoked potentials (EP's) represent a more sensitive measure of brain function and have seen widespread application in the study of human behaviour. As in the EEG paradigm, scalp electrodes are applied to the scalp in order to measure underlying brain activity although EP's are recorded following the presentation of a particular stimulus (visual, auditory or somatosensory). They are particularly useful measures of information processing and the wave pattern offers a number of different indices (components) for analysis.

A study by Prasher, Smith, and Findlay (1990) is the one most commonly referred to in the CFS literature. This study investigated EP's, reaction time and performance measures in 37 CFS patients and 25 unmatched controls. Results showed significant group differences in the reaction time measures and cognitive potentials (*N2* and *P3*) although it was found that the sensory potentials of the visual, auditory brainstem, and median nerve somatosensory systems were unaffected in the CFS patients. The *P300* (an index of attention and speed of information processing) was also abnormal in 48% of the CFS group. One difficulty in the interpretation of this finding is that the *P300* is highly sensitive to mood state and variables such as task difficulty and expectancy set (David, 1991; Wessely, 1993); it is therefore possible that uncontrolled factors such as level of depression could have exerted some influence of the results. Moreover, it is

recognized that a number of extraneous variables can affect *P300* amplitude and latency; these include season of year, blood sugar, and body temperature (Polich et al., 1995) Unfortunately, these do not appear to have been controlled for in the Prasher et al. study.

The possibility of information processing deficits in CFS was more recently (and more thoroughly) investigated in a study by Scheffers, Johnson, Grafman, Dale, & Straus (1992). A battery of psychometric tests (WAIS-R; Wechsler Memory Scale, Beck Depression Inventory and Spielberger Anxiety Scale) was administered to 13 CFS patients and 13 age-matched controls. All psychometric results fell within the normal range. In addition to these measures, evoked potentials and behavioural measures were recorded in response to an attentional task and visual discriminative paradigm. Although slight group differences were found in on a reaction time measure, there were no differences in the EP measures for the two tasks. The authors concluded that information processing capacity (including stimulus identification and perceptual processing) is largely intact in CFS patients. A similar conclusion was reached in a recent (and carefully-controlled) study by Polich et al. (1995). These researchers measured the *P300* using an auditory tone-discrimination paradigm in 25 CFS patients and 25 matched normal controls. There were no group differences for any of the indices recorded (*P300* latency and amplitude, *N1*, *P2* and *N2* components).

Taken together, the small number of studies reviewed above tend to be largely negative in terms of their support for an organic basis to the neurocognitive symptoms reported by CFS patients.

3.2.2 Neuroimaging:

Brain scanning (neuroimaging) has become an exceptionally popular tool in the investigation of structural and functional brain-behaviour relationships, and a variety of sophisticated techniques are available for the clinician and researcher. For example, computerized tomography (CT scanning), nuclear magnetic resonance imaging (MRI), and single photon emission computed tomography (SPECT) have all been used to investigate CFS. The first two techniques (CT and MRI) assess the structural integrity of the brain, whereas the latter two

reflect the metabolic efficiency of the brain (i.e. they are measures of brain function rather than structural integrity).

The use of CT scanning in assessing CFS has resulted in negative findings (Wessely, 1993) although abnormalities have been found using the more sophisticated and higher resolution MRI methodology. For example, the MRI findings of 15 CFS patients are reported by Daugherty et al. (1991); multiple widespread tiny white matter abnormalities (leucoencephalopathy) were found in all patients; in contrast, only one control subject was had similar lesions. The authors argued that such abnormalities can be regarded as atypical since they are dissimilar to those seen in dementia, focal head injuries, multiple sclerosis, systemic lupus erythematosus, and a range of psychopathological conditions. However, they draw a comparison between their study findings and the organic brain syndrome associated with HIV infection. A larger study is reported by Buchwald et al. (1992). Of the 141 patients who underwent MRI, subcortical abnormalities were reported in 78%. The specificity of these findings to CFS is however questionable given that 21% of the control group showed similar findings, and also because similar abnormalities have been found in a variety of diseases including affective disorders (Wessely, 1993). A further point of discredit comes from Reeves, Pellet, & Gary (1992) who question the sample representativeness of the Buchwald et al. study.

Other neuroimaging investigations include those of Natelson, Cohen, Brassloff, and Lee (1993) who compared MRI scans of 52 CFS patients with age- and sex-matched controls. CFS patients were found to have a higher incidence of scan abnormalities relative to controls (27% versus 2%). Increased white matter *T2* signals were found in nine CFS patients and one control, whereas ventricular or sulcal enlargement was observed in five CFS patients. Studies by Strayer et al. (1994) and Schwartz et al. (1994a) also detected MRI abnormalities. The former found white matter abnormalities in 40% of their study group ($N = 89$) while the latter group of researchers detected abnormalities in 8 (50%) of 16 subjects compared to 3 (20%) of 15 age-matched controls (the distribution of abnormalities was widespread but particularly focussed in the subcortical frontal regions). More recently, a study by Suhadolnik et al. (1994) detected evidence of subcortical inflammation in 14 of 15 patients; this is in contrast to Pizzigallo et al. (1996) who found MRI abnormalities (small foci of hypersensitivity) in only 3 of 23 CFS patients (13%).

One of the more interesting MRI studies comes from Cope et al. (1995); these researchers compared the MRI findings of 26 CFS patients (with and without co-existing depression), 18 age-matched normal controls, and 13 depressed psychiatric patients. Results revealed the existence of white matter lesions in a small number of individuals from all three groups (three CFS patients, four depressed patients, and two normals). Although the number of frontal and total lesions correlated significantly with a measure of overall cognitive decline (NART-WAIS-R IQ difference), there was no significant association between the lesions and other neurocognitive measures used in the study. This result tends to suggest minimal effects of MRI-detectable brain lesions on neurocognitive functioning.

It seems appropriate to question the significance of the neuroimaging findings. Firstly, the clinical significance of MRI white-matter lesions has not been well-established. Cope et al. suggest that lesions could indicate a number of conditions (such as areas of arteriolar hyalinisation, the ageing process, focal areas of demyelinization, and small-vessel diseases). Secondly, MRI abnormalities are found in normal individuals as well as in organic and psychiatric conditions. Focal areas of increased signal are most commonly seen in demyelinating, post-infectious and vascular diseases according to Natelson et al. (1993). However, similar findings have also been observed in patients presenting with major affective disorder and have been shown to correlate with increased hospital admissions and depression scores in this group (Cope et al., 1995; Natelson et al., 1993). The results of some of the existing MRI investigations of CFS therefore become difficult to interpret since it is not possible to say whether the deficits would remain following amelioration of the depression or change in clinical condition. The base rates of MRI abnormalities in healthy individuals is also not well-established. Until there have been investigations that correlate MRI indices with changes in CFS symptomatology, it would be wise to conclude that the specificity of MRI findings in CFS remains to be firmly established.

Functional assessment in neuroimaging is made on the basis of administering a harmless radioactive tracer to the subject and then monitoring distribution thereof using a computerized detection system. Both regional cerebral blood flow and glucose metabolism can be studied in this way, and they provide useful indicators of brain function. The dependent measure in the SPECT paradigm is rate of cerebral perfusion (blood flow) and a number of studies have investigated this parameter in CFS patients. A range of SPECT abnormalities have been reported

and include brainstem, frontal, parietal, temporal and occipital hypoperfusion as well as subcortical deficits involving the basal ganglia (Costa et al., 1995; Ichise et al., 1992; Schwartz et al., 1994a; Schwartz et al., 1994b; Wessely, 1993).

The first published SPECT investigation of CFS was conducted by Ichise and colleagues in 1992. They assessed regional cerebral blood flow in 60 CFS patients and 14 normal controls. Significant group differences were apparent, with the CFS patients showing lower than normal blood flow (2 *SD*s below mean) in the frontal, temporal, parietal and occipital regions of affected individuals (63%, 35%, 53% and 38% of cases respectively). More recently, Schwartz et al. (1994a) found widespread cortical and subcortical perfusion defects in 81% of 16 patients compared with 21% of 14 control subjects. These two groups were also differentiated on the basis of site of abnormality, with the CFS group showing a preponderance of lateral frontotemporal and basal ganglia defects. Similar findings are reported in the second Schwartz et al study, although this time SPECT was compared across three patient groups (CFS, AIDS, depression) and one control group of healthy individuals (Schwartz et al., 1994b). All three groups had significantly more defects than healthy controls and these were concentrated in the lateral frontal, lateral temporal and medial temporal lobes. The authors commented that the similarity in defect location may account for the cognitive and affective symptoms (depression, irritability and memory disturbances) common to these patient groups. Although not yet published, the SPECT findings of Goldstein (as cited in Boegman, 1995) include observations that depressed patients have different patterns of decreased blood flow when compared to CFS patients (in depression the pattern is mostly orbitofrontal compared to dorsolateral prefrontal flow reduction in the CFS group). Goldstein interprets this finding as evidence that CFS involves dysregulation of a neural network linking the limbic system and dorsolateral prefrontal cortex.

One difficulty that SPECT shares with MRI is the lack of specificity of findings as they relate to CFS. Although SPECT is easily able to identify functional brain impairment, it is less informative about etiology and pathogenesis. For example, the CNS dysfunction could be due to a primary organic factor or it could be secondary to systemic or psychiatric factors affecting brain function. In terms of lack of specificity, SPECT abnormalities are seen in a range of conditions such as systemic lupus erythematosus, cocaine abuse, multi-infarct dementia and depression (Schwartz et al., 1994b; Wessely, 1993). Similar SPECT findings in CFS and

depression have led to speculation that depressed mood is associated with dysfunction of the frontostriatal axis (this might explain the clinical similarity between these two groups). However, a qualitative difference in the pathophysiology of the CNS defects in these two conditions is hypothesized by Schwartz et al. (1994a). They suggest that the abnormalities in depressed subjects reflect neurotransmitter dysfunction rather than the diffuse inflammatory or vasculitic process which is thought to characterize CFS and conditions such as AIDS. With reference to this latter comparison it is interesting to note that symptomatic comparisons between AIDS and CFS patients have appeared in the literature (e.g. Folks et al., 1993; Komaroff, 1993; Ojo-Amaize, Conley, & Peter, 1994; Smith, 1992) although the differences between the two syndromes seem to be more striking than any similarities (see later comments). Nevertheless, a similar source for neurological dysfunction has been suggested; both CFS and HIV infection are thought to involve a subacute encephalitis characterized by widespread demyelinization. This may be caused by direct viral invasion of the brain substance (Schwartz et al., 1994b).

The most recent investigation of brain perfusion abnormalities in CFS is a study by Costa et al. (1995). Following a pilot study of 24 CFS patients and an equal number of matched controls (Costa et al., 1992), these investigators compared brain perfusion in a further 43 CFS subjects, 40 healthy volunteers, 10 age- and sex-matched epileptics and 29 depressed patients. In the pilot study, all CFS patients showed a generalized reduction in blood flow (although the reduction was greatest in the frontal cortex of both hemispheres as well as the brainstem); no perfusion abnormalities were detectable in the normal volunteers following visual (qualitative) inspection. Together with the pilot group, the additional CFS patients showed lower brainstem perfusion than the depressed controls when brain perfusion differences were analyzed quantitatively using radioactivity ratios. Although the authors were unable to establish causality, they suggested that their study provided a link between commonly reported neurological and cognitive changes in CFS, and areas of the brain potentially sensitive to viral infection from the herpes group of viruses (brainstem and diencephalon). Perhaps the greatest value of this study is that brainstem hypoperfusion appears to be a potentially useful diagnostic index for differentiating CFS and depression.

3.3 OTHER BIOLOGICAL INVESTIGATIONS

In addition to the neuroimaging studies described in the previous section, there have been a few studies that have examined other biological parameters that have relevance for CFS symptoms. For example, noting complaints of dysequilibrium (i.e. disturbed balance and hearing disturbance) in some of his CFS patients, Furman (1991) tested the vestibular function in three such patients. All revealed nonspecific and nonlocalizing abnormalities which were interpreted as evidence of a CNS rather than peripheral deficit.

The investigation of sleep disturbances in some CFS patients has been undertaken in a number of recent publications. Using a combination of self-report and EEG methods (polysomnography), Morriss et al. (1993) found a high incidence (58%) of sleep disorders in their sample of 12 patients. Additional findings of this study were that individuals with CFS were more likely to spend greater time in bed, sleep less efficiently, and suffer from either insomnia or hypersomnia than control group subjects. A study using similar methodology is reported by Buchwald, Pascualy, Bombardier, and Kith (1994). Results indicated that 81% of 59 CFS had at least one sleep disorder, the most common being sleep apnea[32] (44%) and hypersomnia (12%). Recent research by Le Bon, Fischler, Hoffman, Meirleir, and Cluydts (1996) found that of 54 randomly selected CFS patients, 6 to 46% presented with a sleep apnea (depending on how this was defined), while 30% complained of excessive daytime sleepiness. Despite the high incidence of sleep disorders, Le Bon et al. were unable to establish a causal relationship and concluded that the fatigue of CFS patients is not related to a primary sleep disorder. The existence of a reciprocal relationship between the immune and sleep-wake systems has recently been uncovered in a study by Moldofsky (1993). He suggests that disordered regulation of the cytokines (IL-1, IL-2, and interferon) provokes alterations in the immune and sleep-wake systems of CFS patients. The significance of these complex interactions awaits further research.[33]

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The relevance of sleep apnea for CFS stems from the notion that unrecognized hypoxia could contribute to the onset of CFS either by impairing metabolic processes such as phosphorylation and ATP production, or alternatively, by impacting on neuroendocrine functions.

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In a review of the 1995 World Meeting on CFS, Boegman (1995) reports that when laboratory animals are kept awake, they eventually die of septicaemia due to disturbed immunity.

Electroautonography (EAG)[34] has also been used as a diagnostic technique in the study of CFS. Lerner (1996) investigated the skin potentials of 50 healthy individuals and compared these with the EAG recordings of 10 CFS patients who met the CDC criteria. Asymmetrical skin potentials and other abnormalities were more prevalent in the CFS group, leading Lerner to conclude that CFS is a disorder of the autonomic nervous system. This avenue of research also awaits further study.

3.4 THE PATHOPHYSIOLOGY OF FATIGUE (THE MUSCLE VERSUS BRAIN DEBATE)

There can be little doubt that patients with CFS experience a sense of fatigue. Indeed, post-exertional malaise, muscle weakness and myalgia are reported by 50-95% of patients (Komaroff, 1993). It is therefore not surprising that the muscle systems of the body have been the focus of interest for some researchers; the aim has been to investigate the nature of muscle fatigue using various physiological methods.

For the physiologist, fatigue "represents a failure to sustain the expected muscular force" (Swartz, 1988 p. 1726). Such failure could potentially occur at any point between the cerebral cortex and the muscle fibre, and is generally referred to as central fatigue. Central fatigue is defined as the "failure to achieve and maintain the recruitment of high threshold motor units" (Edwards, Newham, & Peters, 1991, p. 833) and is considered to represent a "failure of neural drive" (Edwards, Gibson, Clague, & Helliwell, 1993, p. 103). Potential causes of central fatigue include pathologic processes, decreased effort in muscle activation due to pain, decreased motivation and/or impaired concentration (Kent-Braun, Sharma, Weiner, Massie, & Miller, 1993). Peripheral fatigue is a term generally reserved for fatigue that occurs in the muscles and is due to impaired neuromuscular transmission (Lewis & Haller, 1991). It has been described as

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Electroautonography (EAG) involves the recording and interpretation of electrical skin potentials on the hands and feet, and is technically a measure of the state of the autonomic nervous system. While galvanic skin measurements have a long history in psychophysiology, it seems that the EAG is a recent attempt to market a revised system of recording and interpretation. Since EAG has not yet seen widespread use, it is difficult to comment on the validity of the procedure developed by Lerner.

"a failure of force generation in whole muscle" (Edwards et al., 1993, p. 103). Representative medical conditions leading to peripheral muscle fatigue include myasthenia gravis, congestive heart failure and mitochondrial myopathies (Swartz, 1988).

The distinction between central and peripheral fatigue has led to the "brain versus muscle debate" in the CFS literature. Essentially, the argument is operationalized in research that attempts to explain fatigue as a peripheral muscle problem, as opposed to research that explains fatigue on the basis of abnormal central (brain) activation. Such activation is represented by central motor conduction (i.e. of the corticospinal motor neuron network). Notwithstanding this argument, these two types of fatigue can be differentiated upon laboratory testing. A range of techniques may be utilized by the physiologist interested in studying central or peripheral fatigue. These include: investigations of muscle histopathology (biopsy); physical output measures (such as maximal voluntary isometric contraction force); systemic exercise capacity (monitored in terms of blood oxygen consumption and lactate levels); electromyography (assesses muscle action potentials); nerve conduction (using evoked potentials); cell metabolism (using magnetic resonance spectroscopy); and tests of membrane function.

Research into the muscle histopathology and physiology in CFS patients has produced some mixed findings. Although clinical examination of muscle bulk is usually normal (Peters & Preedy, 1991), histological and metabolic abnormalities (such as a decrease in muscle protein synthesis) have been reported in some studies (Behan & Behan, 1985; Jamal & Hansen, 1988; Kuratsune et al., 1994; Preedy, Smith, Salisbury & Peters, 1993; Ramsay, 1978) but not in others (Edwards et al., 1993; Kent-Braun et al., 1993). One problem that plagues research of this nature, is that structural and metabolic abnormalities are known to accompany physical deconditioning and so some degree of abnormality is hardly surprising in largely sedentary, often bed-ridden CFS patients (Klonoff, 1992). Current opinion appears to be that these abnormalities are both subtle and non-specific, and therefore unrelated to the experience of fatigue (Bearn & Wessely, 1994; Edwards et al., 1993).

In an investigation of possible CFS-related abnormalities in muscle structure and function, Edwards et al. (1993) conducted muscle biopsies on 108 CFS patients and 22 healthy volunteers. They failed to find any consistent association between CFS symptoms and changes in fibre type

prevalence, fibre size, degenerative or regenerative features, glycogen depletion, or mitochondrial abnormalities (mitochondria represent the energy processing units of cells). Karutsune et al. (1994) on the other hand, found low serum levels of carnitine in 38 CFS patients. Since carnitine is necessary for mitochondrial energy production, these investigators felt that their findings could offer at least a partial explanation for reduced mitochondrial function in CFS.

Single-fibre electromyography (EMG) is an investigative technique that assesses the overall integrity of neuromuscular transmission. More specifically, it examines the "temporal synchrony of activation of the individual muscle fibre components of the same motor unit" (Jamal & Miller, 1991, p. 817). Abnormalities (defined as prolonged "jitter") in CFS patients are reported in some of the early studies (e.g. Jamal & Hansen, 1985; Richardson, 1978) although subsequent and more sophisticated investigations have failed to confirm these early findings (Edwards et al., 1991; Kent-Braun et al., 1993; Roberts & Byrne, 1994). One notable exception is a study by Connolly, Smith, Doyle, and Fowler (1993) in which single fibre electromyography was performed on 35 CFS patients. The subjects in this study were further categorised as having an acute-onset post-viral fatigue syndrome, a non-specific chronic fatigue, or possible muscle disease (in view of presenting myalgia). Non-specific abnormalities in fibre density were detectable in 6 of the 11 myalgic patients, although all demonstrated normal creatine kinase levels.

To consolidate thus far, it appears that although delayed or slowed physiological muscle recovery has been hypothesized as an explanation for persistent fatigue and myalgia in CFS patients, this has not been consistently demonstrated by existing EMG investigations. Nerve conduction studies have also failed to demonstrate any abnormalities in CFS patients (Currie & Shelkov, 1978; Jamal & Miller, 1991).

Nuclear magnetic resonance (NMR) spectroscopy has been employed by a number of researchers interested in assessing the biochemical basis of CFS. This technique looks at changes in intracellular pH and inorganic phosphate (both indices of muscle metabolism) as a result of carefully monitored exercise. Despite initial reports of excessive muscular acidosis following exercise in fatigued patients and attempts to link this with a viral etiology (Yonge, 1985), findings of impaired exercise capacity have not been confirmed in later studies (Kent-Braun et al., 1993;

Jamal & Miller, 1991). For example, Jamal and Miller (1991) found no difference between CFS patients and controls in terms of exercise-induced muscle metabolism, despite claims by the CFS patients of higher perceived effort. According to Bearn and Wessely (1994), prevailing opinion is that the muscle fatigue reported by CFS patients does not have a peripheral biochemical basis.

The exercise capacity of CFS patients has been investigated in a number of studies (Edwards et al., 1993; Fulcher & White, 1996; Joos, Meeusen, De Becker, Dendale, De Meirleir 1996; Kent-Braun et al., 1993; Lloyd, Gandevia, Brockman, Hales, & Wakefield, 1994; Lloyd, Hales, & Gandevia, 1988; Lewis & Haller, 1991; McCluskey & Riley, 1992). The parameters of interest to such investigations have included measurement of heart-rate, perception of effort, muscular strength, oxygen uptake (oxidative metabolism), cytokine production and anaerobic metabolism. Again, there is little to suggest that CFS patients function any differently from normal controls, although Kent-Braun et al. (1993) report a muscle activation failure in their sample of seven CFS patients. This was manifested as a progressive failure to fully activate the muscle during strenuous exercise. The authors interpreted this as evidence of a voluntary failure in muscle activation (i.e. due to central factors). Using a treadmill, McCluskey and Riley (1992) compared a group of CFS patients with a normal sedentary control group, and a group of patients with irritable bowel syndrome. Measurements included heart rate, respiratory gas exchange and end-tidal CO_2, in addition to subjective reports of fatigue. A lower exercise capacity as well as increased reports of perceived fatigue was evident for the CFS patients. The findings also indicated that the pattern of physiological response in the CFS group was similar to that normally encountered in unfit or deconditioned individuals. The interpretation made by these authors was that physical deconditioning may partially account for the chronic fatigue in CFS. Some support for this latter finding comes from Fulcher and White (1996), and Joos et al. (1996); the latter found very low maximal and submaximal work output in 100 CFS patients (resting pulse was found to be high at 90 bpm ± 14). Following an individually-tailored exercise program consisting of 5 to 20 minutes of daily exercise, improved aerobic fitness was observed at a six-month follow-up.

Lloyd, Phales, et al. (1988) measured muscle performance (elbow flexors) in a group of CFS patients and compared them to normal controls. Both groups revealed similar muscular strength, although the CFS patients took longer to recover their force-generating capacity; a

finding that was interpreted as evidence of abnormal perception of effort and which resulted in a restriction of physical activity. A more recent study by Lloyd and colleagues examined cytokine production in response to prolonged isometric exercise in 12 male CFS patients. Cytokines (e.g. interleukin-1 and interferon-alpha) are released into the bloodstream in response to exercise, and they act on CNS targets. Results suggested no significant difference in cytokine production between the CFS patients and healthy controls. However, these investigators did find a high level of subjective fatigue in the CFS group that did not change in the face of physical activity. Interestingly, the CFS group demonstrated improved mood and enhanced cognitive ability following exercise, a finding that is at variance with subjective complaints by some patents. This was attributed to the possible exercise-induced production of anti-stress neurochemicals (cortisol and endorphin). The interaction of these neurochemicals with brain cells that are functioning at less than optimal efficiency was posited as an explanation for prolonged fatigue in CFS patients (Lloyd et al., 1994).

In an attempt to investigate possible abnormalities in the strength and constancy of central motor impulse in CFS patients (this would enable researchers to assess claims of increased central activation), Brouwer and Packer (1994) examined the characteristics of the responses evoked by transcranial magnetic stimulation (TMS) in relaxed and voluntarily active muscles of 17 patients. Results suggested an exaggeration of perceived fatigue in the CFS group (a finding compatible with similar research); however, these authors could not exclude the possibility that this finding was secondary to unstable cortical excitability. Hopefully, continued research will clarify the nature of this corticospinal excitability and origin of perceived fatigue.

To summarize, it may be stated that the search to find a physical or peripheral basis to the fatigue in chronic fatigue syndrome has generally resulted in negative findings; i.e. there appears to be no difference between CFS patients and healthy controls in terms of muscle fatigability. It seems safe to conclude therefore, that CFS is not a myopathy. Stated differently, the evidence appears to argue for a central basis to CFS (i.e. one in which there is abnormal perception of muscle exertion as opposed to actual muscle pathology).

3.5 IMMUNE SYSTEM FUNCTIONING IN CFS

The study of immune system functioning has occupied a central position in the biological research into CFS, and there is accumulating evidence that immunologic factors are important in the development of CFS. Before reviewing this and the material in subsequent sections in detail, it is important to emphasize the dynamic relationship that exists between the immune system, nervous system and behaviour. This relationship comprises the relatively new field of study known as psychoneuroimmunology (Maier et al., 1994). Psychoneuroimmunologists recognize that the immune system does not operate in an independent fashion, and there is evidence that a bidirectional regulatory relationship exists with the CNS. For psychologists, the relevance of this relationship is important; immune processes can indirectly influence behaviour, and *vice versa*.

As far as the CFS literature is concerned, the most popular contention is that symptomatology develops in response to a viral trigger (Goldstein, 1993); however, Lloyd and Klimas (1994), on the basis of their review of appropriate immunological studies, conclude that it would be premature to draw any firm conclusions. Part of this concern stems from the multiple confounding variables that are known to characterize this type of research. These include: sample heterogeneity; methodological differences in laboratory procedures; and confounding variables such as the effects of medications and mood alterations on immune parameters (ibid). Before reviewing the relevant immunologic findings in CFS, a brief description of the immune response seems appropriate.

Viruses may invade a number of bodily systems during acute infection. For the most part, the primary targets are cells of the CNS, skin, respiratory tract and gastrointestinal tract. However, there may be preferential invasion of the immune system cells, especially by members of the herpes virus and retrovirus families (Griffin, 1991). When the human body is faced with a bacterial or viral infection, it mobilises a defence (immune response)[35] which is designed to remove the invading agent and destroy any infected cells (Roitt, 1971). Various somatic systems

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35

There are two types of immunity: *innate* and *specific(acquired)*. The former refers to our inherited resistance to pathogens: it operates in a non-specific way (examples include skin acidity, mucous generation, and local inflammation). The latter is acquired through recognition (and subsequent destruction) of foreign substances (antigens); T and B lymphocytes are critical components of this type of immune response. Specific immunity is a delayed process, often requiring five or more days to generate antibodies in order to destroy particular antigens.

are involved in the immune response and include the lymph nodes, spleen, bone marrow, tonsils, thymus, appendix and small intestine (Hayes, 1995). The circulatory system provides a means of communication. A number of different cell types comprise the immune system; components include neutrophils, monocytes, eosinophils, basophils and lymphocytes (including B, T, and natural killer subtypes). Lymphocyte activity is generally regarded as an index of immune system status (ibid). Once activated, the immune response is variable depending on the type and nature of infection; global alterations of various bodily systems follow more severe infections, whereas less severe infections tend to precipitate more circumscribed local changes (perhaps involving the lymph nodes). A simplistic linear relationship between antigen challenge and subsequent immune response is not apparent; rather it should be viewed as:

> a process that extends over many days and require complex coordination between many different types of cells that have to interact with each other in very circumscribed ways. It is a dynamic process over time, not a discrete or punctuate process (Maier et al., 1994; p. 1005).

In general, the activation of the immune system is represented by the following:

> (1) The mobilization of various immune cells (antibodies) to counter the invasion of foreign intruders (antigens or pathogens). These antibodies (which include lymphocytes, macrophages, and natural killer cells) bind to the offending agent and block attachment of antigens to susceptible cells; they also function to kill infected cells. Various lymphocytes exist; two of the most important are T and B lymphocytes (Maier, Watkins, & Fleshner, 1994). T cells circulate through various body systems (blood, spleen, lymph glands) until they are activated by a cytokine called interleukin-1 (see below). Activated T-cells in turn release interleukin-2 which assists in the multiplication and maturation of specialized T-cells (i.e. those designed to counter a specific antigen challenge). This process takes several days.
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> (2) The synthesis of immunoglobulins (these are soluble peptide molecules produced and regulated by the immune cells and they are also considered to fall under the label of antibodies or immune complexes). Immunoglobulins have various functions such as

neutralizing bacterial toxins, and one way in which a virus can be neutralised occurs when it is "coated" by an antibody working alone or in conjunction with other antibodies (Alexander & Good, 1977). The processes involved in this response are complex and the reader is referred to any standard text on immunology such as *Fundamentals of Clinical Immunology* (Roitt, 1971) for additional information. It may be noted however that there are five classes of immunoglobulins. These are immunoglobulin G (commonly referred to as IgG), immunoglobulin A (or IgA), immunoglobulin M (IgM), immunoglobulin D (IgD), and immunoglobulin E (IgE). Generally speaking, a systemic viral infection will give rise to an initial rise in IgM antibody followed by an increase in IgG and IgA antibody levels. Prolonged immunity is associated with raised IgG levels (Alexander & Good, 1977). In other words, the IgG subclass is responsible for keeping viral infections in check. IgA is considered to be part of the first-line defence against upper respiratory tract infections (Chase, 1991).

(3) The release of specialized proteins known as cytokines which have the capacity to direct (i.e. activate or inhibit) the response of other cells of the immune system. Essentially, they enable macrophages to devour bacteria and other foreign material (Twombly, 1994).

Two particular cytokines which have been of interest to researchers are interleukin-1 (IL-1) and interleukin-2 (IL-2). Other cytokines which play a role in mediating the immune response include the interferons (IFN) which are specialised proteins, and tumour necrosis factor (TNF). Interferon is regarded as the body's most rapidly produced defence against viral invasion (McDonald & Mann, 1991), and there are three types: alpha (α), beta (β) and gamma (γ). Interferons do not inactivate viruses, but rather protect cells by interfering with viral protein synthesis. Patients with acute viral illnesses typically have high levels of circulating interferon, and it has been used as a therapeutic agent in the treatment of cancer, hepatitis B, herpes simplex keratitis, varicella zoster (shingles) and HIV infection. Unfortunately it has significant side-effects (fever, headache, malaise, myalgia and neurocognitive disturbance) and so has seen little use in the treatment of CFS (Adams, Quesada, Gutterman, 1984; Mowbray & Yousef, 1991; Smedley, Katrak, Sikora, & Wheeler 1983).

Interleukin-1 is one of the few molecules that can cross the blood-brain barrier, and there are receptors in the hypothalamus (Arnason, 1991). One consequence of activation of these receptors is fever, which is characteristic of infection and immune system activation. A second consequence is the release of CRH from the hypothalamus and subsequent elevation of ACTH and cortisol levels (this is characteristic of an immune response). Like interferon, IL-2 is used as a treatment for cancer, but can produce flu-like symptoms that includes severe cognitive impairment (Moldofsky, 1993). Thus, while cytokines and interferon are regarded as being essential for effective immunity, they also lead to clinical symptoms by virtue of their physiological actions. Weakness, listlessness, fatigability, myalgia, hypersomnia, anorexia and social withdrawal have all been reported as responses to an infective process (Bearn & Wessely, 1994). The resemblance of these symptoms to those found in CFS is striking, and the sustained release of cytokines in some CFS patients[36] is thought to deplete the efficacy of the immune system and contribute to ongoing CFS symptomatology (Suhadolnik, 1994).

Immune system involvement in CFS is not a new concept and was proposed as early as 1985 (Behan & Behan, 1985). The exact nature of the dysfunction is not entirely clear although and this lack of clarity is hardly surprising given the complexity of the interaction between viruses and the immune system (Alexander & Good, 1977). Nevertheless, elevated numbers and altered functioning of natural killer (NK) cells, as well as elevated titres of IgG antibody to EBV in some patients, appear to be the most consistent findings (Arnason, 1991; Griffin, 1991). In nine studies reviewed by Buchwald and Komaroff (1991), an average of 31% of patients (range 4 to 100) were found to have decreased amounts of immunoglobulins of the IgG, IgA, IgM, or IgD classes. However Gupta and Vayuvegula (1991) reported generally normal levels of immunoglobulins in their sample of 20 CFS patients. Rasmussen et al. (1994) also noted that the apparent reduction of IgA and IgE concentrations in their CFS sample was relative rather than absolute, owing to comparative elevation of these immunoglobulins in the control group (i.e. above the upper limit of the normal range).

Additional immune system abnormalities reported in the literature include: a reduction

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36

Unpublished observations by Bell (1994) suggest that over 70% of CFS patients have abnormal levels of IL-2.

in the number of T lymphocytes, including CD2 (total number), CD4 (helper/inducer),[37] and CD8 (suppressor/cytotoxic) subsets; dysregulation of TNF; increased T-cell mediated suppression; decreased or increased production of interleukin (IL-1 and IL-2) and interferon; elevated levels of circulating immune complexes; and a high rate of skin test reactivity to common food or inhalant extracts (Abbey & Garfinkel. 1991; Barker, Fujimura, Fadem, Landay, & Levy, 1994; Lloyd, Hickie, Hickie, Dwyer, & Wakefield, 1992; Kroenke, 1991; Lloyd et al., 1992; Patarca, Klimas, Lugtendorf, Antoni, & Fletcher, 1994; Spracklen, 1988; Shafran, 1991). Some of these abnormalities. as well as others not specifically mentioned above, are summarized in Table 3-1.

TABLE 3-1. Immunologic Abnormalities Reported in CFS

Elevated titres of antibodies to viral proteins
Hypo- or hypergammaglobulinemia
Increased or decreased circulating immune complex levels
Decreased immunoglobulin production in vitro
Increased leukocyte2',5' oligoadenylate-synthetase
Decreased interleukin-2 production in vitro
Increased serum interleukin-2 levels
Decreased gamma-interferon synthesis in vitro
Increased T-helper/T-suppressor cell ratios
Increased T-cell suppression of immunoglobulin synthesis in vitro
Decreased or increased natural killer cell activity
Decreased antithyroid antibody levels
Variable antinuclear antibody levels

(Kyle & deShazo, 1992, p. 31)

Inter-study methodological variability and a lack of specificity to CFS makes interpretation of these findings difficult. Swanink et al. (1996) failed to replicate previously

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[37] Interestingly. Bell (1994) draws a comparison between CFS patients and immuno-compromised patients who have been suspected of being HIV-positive but who subsequently prove to be HIV-negative; both show low numbers of CD4 lymphocytes. Although CFS and AIDS are two distinct illnesses with different transmission modes, it is possible that both are caused by retroviruses (chronic disease with altered immunity are characteristic features of retrovirus infection). Fatigue is a further commonality, with approximately 20-60% of HIV infected patients reporting its presence (O'Dell et al., 1996) . Bell is of the opinion that severe CFS and the syndrome which has come to be referred to as "antibody-negative AIDS", may ultimately be found to share a common etiology.

reported immunologic abnormalities or find a correlation between immunological profiles and clinical symptomatology. In contrast, Ojo-Amaize et al. (1994) found an association between symptom severity and NK activity, although a relatively small sample of patients was used (N = 13). A range of immunological abnormalities was reported by Keller et al. (1994), and included viral reactivation profiles in all CFS patients (N = 110) as well as evidence of decreased NK cells and increased levels of T cells and IL-2. However, Tirelli, Tavio, & Pinto (1996) are of the opinion that immunological abnormalities, when present, occur only in a small proportion of patients.

Alterations in immune system functioning may be precipitated by a variety of psychological factors, most notably acute stress and depression (Armon & Kurland, 1991; Evans, 1991; Kennedy, 1991). Generally speaking, stress has been correlated with elevated lymphocyte counts and lowered T, B, and NK cell counts (Hayes, 1995). A review of the anecdotal and clinical research that relates depression to altered immune response and increased risk of illness, is presented by Dorian and Garfinkel (1987). Specific findings include impaired cell-mediated immunity, accompanied by a decrease in the number of lymphocytes and reduced NK cell activity (Gold et al., 1990; Schleifer et al. 1984). Abbey and Garfinkel (1991) maintain that these changes may not be present in all cases. The idea that depression and CFS may share some common pathophysiological mechanisms in terms of immunological dysfunction, has been a commonly held notion (Hickie et al., 1990; Komaroff & Klimas, 1994; Wakefield & Lloyd, 1987). Indeed, many view CFS as an atypical depressive disorder (Gold et al., 1990; Greenberg, 1990; Kruesi et al., 1989; Taerk et al., 1987).

Differences in the immune system profiles of depressed versus CFS patients have been reported. One parameter of interest is cell-mediated immunity (CMI). This refers to a hypersensitivity reaction encountered in many allergic reactions to bacteria, viruses and fungi. Usually a skin test is used to introduce an agent to which a healthy immune system will respond with erythema and induration (Roitt, 1971). Lloyd et al. (1992) investigated CMI in 20 CFS patients and compared results with 20 sex-matched depressed controls and a further 20 healthy controls. Significantly more CFS patients showed abnormal immune system responses (as measured by a delayed type hypersensitivity skin test) than either of the two control groups. The authors interpreted this as evidence that altered immunity could not be attributed to concurrent

depression. Some support for this finding also comes from a study by Hickie et al. (1992) in which 88% of CFS patients ($N = 33$) revealed evidence of abnormal cell-mediated immunity. Psychological status was assessed prior to and after a placebo-controlled trial of high dose intravenous immunoglobulin. Only those patents who received active immunotherapy showed a consistent correlation between improvement in depressive symptoms and improved immunological status. A failure to find any significant pre-treatment association between depressive symptoms and immunological abnormalities in this study led these authors to conclude that CFS patients are more likely to exhibit a secondary rather than primary depression.

To conclude this section on immune system functioning, current opinion suggests that many CFS patients have a disordered immunological response (Lloyd & Klimas, 1994; Keller et al., 1994). What is less clear, is the exact cause of disordered immunity; is it due to viral infection or to psychological and physical reactions to a subclinical infection? Is it possible for viral persistence to occur within a cell without alteration of its basic integrity? An interpretative difficulty in the proposed viral basis of CFS is therefore apparent; viral assays are not able to reliably distinguish between primary viral infection, non-specific suppression secondary to physical ill health, and changes consequent upon the emotional effects of chronic fatigue (Denman, 1990). Although early studies were able to make a link between persistent EBV infection and CFS, subsequent findings have questioned this association on the basis of evidence supporting the reactivation of a number of different viruses in CFS (Lloyd, 1994). For example, varicella, rubella, mumps, cytomegalovirus (CMV) and human herpesvirus type 6 (HHV-6) have all been implicated in CFS, although it is unclear whether they are precipitants or epiphenomena (see Chapter 1). In the study by Keller et al. (1994), all patients showed a reactivation of either EBV, CMV or HHV-6. However, EBV antibodies are also commonly found in individuals diagnosed with stress conditions and depression (Evans, 1991). This lack of specificity in causation suggests only that these various conditions may reactivate a previous EBV infection leading to a chronic condition (CEBV).

One interesting aspect of the notion of viral-induced abnormal immunity in CFS, is the commonality of symptoms that CFS shares with other viral conditions. For example, symptoms of malaise, fever, muscle pain, headache and sore throat appear to be shared not only by the viruses implicated in CFS (i.e. EBV, CMV, HHV-6), but also measles, HIV, and the more

recently described Ebola virus (Griffin, 1991; Lloyd et al., 1993; Reeves & Urquart, 1996). Together, the shared symptoms of these infections suggest some degree of commonality of the processes involved in the behavioural manifestation of immune system dysfunction.

Finally, the recognition that most immunologic activities involve complex interactions among a number of cell types and their products, as well as a failure to establish discrete effects, are definite sources of confounding in the CFS research (Herberman, 1991; Miller, 1991; see also later comment by Maier et al. 1994). Nevertheless, the degree of variability in the findings of these studies of immune system functioning might explain some of the variability in CFS symptomatology. As a closing comment, Demitrack (1994) proposes that "the clinical overlap between CFS and a variety of primary psychiatric illnesses may reflect the involvement of a sequence of final common biological events which may be similarly dysregulated by a wide array of infectious or non-infectious antecedent events" (p. 2).

3.6 BIOLOGICAL ASPECTS OF PSYCHONEUROIMMUNOLOGY

The idea that immune system functioning can be influenced by psychological factors and environmental stress was introduced in the previous chapter. The exact mechanisms through which environmental and psychological stress may influence immune system functioning, provides a major research interest for those working in the field of psychoneuroimmunology. Comprehensive reviews of this complex field are presented by Maier et al. (1994) and Ader, Cohen, & Felten (1995); the reader is referred to these articles for a more complete account than can be offered below.

The basic premise of psychoneuroimmunology recognizes that the immune system does not function independently, but that interactions occur between behaviour, the brain and the immune response. Essentially, the emerging view is that the immune system is under neural control. In this regard, it may be noted that brain is connected to the immune system via two pathways: (1) directly via the autonomic nervous system; and (2) the neuroendocrine system (via the pituitary).

(1) *autonomic nervous system*:

With regard to direct innervation of the immune system, it is known that some sympathetic nerve fibres terminate in structures which contain lymphocytes, macrophages etc. (e.g. lymph nodes, thymus, bone marrow), and that these cells of the immune system are responsive to neurotransmitters such as noradrenaline and substance P (both have the capacity to influence the activity of immunoglobulins, T-cells and NK cells). In this way, the activity of lymphocytes and macrophages may be influenced by the secretion of epinephrine and norepinephrine. The idea that the brain can regulate the functioning of the immune system has support from animal research; animals with bilateral anterior hypothalamic lesions generally manifest deficient immune responses, whereas those with bilateral posterior hypothalamic lesions occasionally show augmented immune responses (Arnason, 1991). As mentioned, pathways between the immune system and brain are considered to be bidirectional; for example, activation of the immune system causes changes in hypothalamic, autonomic and endocrine processes (e.g. immune system activation increases the firing rate of neurons in the hypothalamus at the time of peak antibody production). Likewise, the cytokines released by activated immune cells are known

to be endocrinologically, electrophysiologically and behaviourally active (the sympathetic nerves have receptors for cytokines).

(2) *neuroendocrine system:*

Many components of human behaviour (such as appetite, sexual behaviour and mood regulation) are determined by the level of hormones present in our bloodstream. These hormones fall under the control of two main structures in the brain; the hypothalamus and the pituitary gland. Cortisol, a corticosteriod hormone (these are otherwise referred to as glucocorticoids and sometimes as stress hormones)[38] is secreted by the adrenal cortex in response to stimulation by adrenocorticotropic hormone (ACTH). This in turn, is released from the pituitary gland in response to the corticotropin-releasing factor (CRF) which is secreted by the hypothalamus. A number of neurotransmitters control the release of CRF: acetylcholine; serotonin; enkephalins; GABA; and norepinephrine. It might be noted that the body's immunity is altered by the action of these various hormones and neurotransmitters, which together act on lymphocyte receptors.

The hypothalamus and pituitary operate to monitor and control the levels of various hormones in the body, and they form part of a network or system referred to as the hypothalamic-pituitary-adrenal (HPA) axis. This system also includes the various neurotransmitter pathways which link the various hormonal structures (such as the adrenal glands) with the brain. Regulation is maintained by a complex feedback system that allows for precise adjustments in hormone levels to be made. The prevailing view of this branch of CFS research is that a reduction in plasma and urinary glucocorticoid levels (i.e. low cortisol) is characteristic of CFS patients, and is caused by a failure in the central (i.e. brain) activation of the HPA axis (Demitrack, 1994; Wessely, 1993). More specifically, this failure in activation can be traced to CRF insufficiency, either through direct effects upon the CNS or indirectly by causing glucocorticoid deficiency (Demitrack & Greden, 1991).

Part of the interest in HPA axis dysfunction in CFS evolved from research into mood disorders (such as depression) and viral infection (such as viral hepatitis and HIV); both are known to alter the integrity of the neuroendocrine system (Bearn & Wessely, 1994; Demitrack,

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38

the existence of high levels of these hormones in the blood is often interpreted as an indication of stress

1994). With regard to depression, abnormalities (i.e. hypersecretion) in cortisol metabolism have been found. and Wessely (1993) reports that stress-induced sensitivity (activation) of the HPA axis may be a precipitant of depression. It also known that various viral infections activate the HPA axis and that changes may continue long after the infection has resolved (Demitrack, 1994). Given the general acceptance that CFS represents a lasting and specific immune dysfunction induced by a viral trigger (Arnason, 1991; de la Torre, Borrow, & Oldstone, 1991), it is logical that research into CFS should consider the links between the immune system and components of the HPA axis. Stress has also been implicated in HPA axis activation by causing an increase in circulating glucocorticoids and an alteration of immune function; this may lead to increased susceptibility to infection and cancer (Ader et al. 1995).

One of the clues which led investigators to the HPA axis in CFS was the clinical observation that many of the symptoms which accompany CFS (e.g. appetite changes, sleep disturbance. elevated body temperature, night sweats, reduced libido, and depression) are suggestive of hypothalamic dysfunction (Wessely, 1993). Various studies have found evidence of this dysfunction which is mediated by neurotransmitter function, and is manifested as an up-regulation (increased sensitivity) of hypothalamic 5-hydroxytryptamine (5HT) receptors in CFS patients (Behan & Bakheit, 1991; Bakheit et al., 1992; Demitrack et al., 1991). The consequence of this impaired activation is manifested clinically as lethargy and fatigue (Demitrack et al., 1991). From the standpoint of neurotransmitter function, 5HT receptors are involved in central serotonergic transmission and mediate a number of CFS-linked functions that include the regulation of sleep. appetite, pain and inflammation (Bearn & Wessely, 1994). It might also be noted that brain 5HT abnormalities have been implicated in a range of psychiatric disorders including depression, anorexia and bulimia nervosa, post-traumatic stress disorder, obsessive-compulsive disorders, primary fibromyalgia syndrome, and physically- or emotionally-induced stress reactions (ibid). Of interest in this regard, is the frequent report by CFS patients that symptom onset followed a significant period of stress. Nevertheless, there are studies indicating that CFS is biologically different from disorders such as depression. For example, Cleare et al. (1995) compared HPA axis and central 5-HT function in 10 CFS patients, 15 depressed patients and 25 healthy controls. Results showed that depression was associated with *reduced* central 5-HT neurotransmission whereas CFS was associated with *increased* 5-HT function. The authors suggested that these distinct profiles may explain some of the behavioural differences between

the two conditions. Although researchers such as Bearn and Wessely (1994) have speculated that dysfunction in other neurotransmitter pathways may exist (e.g. noradrenaline metabolites), these have not yet been systematically explored in CFS.

In supporting the work of others implicating the HPA axis, Goldstein (1993) describes CFS as "a limbic encephalopathy in a dysregulated psychoneuroimmunologic network" (p. 12). Specifically, he believes that the limbic system (and associated cortex) acts as a neural regulator of a range of visceral and neuroendocrine functions involved in CFS (e.g. arousal, sleep-waking, temperature regulation etc.). The basic premise is that CFS symptoms arise from cytokine dysregulation. He cites research showing that the medial temporal lobe (and especially the hippocampus) has the highest concentration of IL-1 receptors in the brain, and suggests that the fatiguing malaise and flu-like symptoms associated with CFS can be localised to this area.[39] In his thesis, he proceeds to relate a wide range of reported CFS symptomatology to a dysfunctional limbic system; however his ideas, if valid, are still to gain acceptance from the wider CFS scientific community.

What should be evident from the material presented above, is that a highly complex relationship exists between the immune system and neuroendocrine system. The psychological modulation of immunity adds another variable, and as we have seen in the previous chapter, a wide range of stressors can lead to altered immunity. Again, complexity exists in this chain of events, leading us away from a simple interpretation that thought and emotions can influence immunity. In this regard, Maier et al. (1994) points out that different stressors produce different combinations of autonomic activity and hormone interactions. In addition, personality factors and coping strategies act as modulators of stress-induced immune response. As a result of this knowledge, Maier et al. caution investigators against drawing hasty conclusions from data that measures discrete aspects of immunity at single points in time; they comment:

> the immune system contains a high degree of redundancy, and so the fact that an event might alter an intermediate product or step does not provide convincing

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[39] According to Goldstein, "fever is probably caused by cytokines such as IL-1 which have a dense receptor population in the anterior hypothalamus" (p. 79). He then suggests that disorders of temperature regulation (including night sweats and intermittent mild fevers) are associated with hypothalamic dysfunction.

information about whether the event in question would impact on a normal endpoint of the immune response (i.e. the production of antibody) (p. 1009).

Having considered the mechanisms for CNS influence on the immune system, it is important (in terms of the bidirectional relationship) to briefly mention events in the opposite direction, i.e. the immune modulation of CNS activity and behaviour. A critical component of the feedback loop appears to be the cytokines (particularly IL-1) which, when released, can cause electrophysiological changes in the brain as well as neural metabolism of norepinephrine, serotonin and dopamine (Maier et al., 1994). IL-1 can also decrease thyroid function and increase slow-wave (delta) sleep (Goldstein, 1993). Furthermore, immune system activation creates a pituitary-adrenal response equivalent to a stress response and this can be achieved artificially in a laboratory setting through the administration of IL-1. Behavioural responses include altered pain thresholds and changes in emotional reactivity (Maier et al., 1994). Of importance to the current study are the potential neurocognitive effects of immune system activation. For example, IFN administration has been found to result in slowed thinking, diminished arousal and concentration, and memory disturbance (Adams et al., 1984). EEG changes (notably slowing) have also been documented in a couple of studies (Mattson et al., 1983; Smedley et al., 1983). All of these effects were found to be reversible following cessation of IFN administration. With regard to IL-2 administration, Denicoff et al. (1987) found dose-related impairment on a range of neuropsychological measures. One recent study by Lutgendorf et al. (1993) attempted to correlate CFS-induced cognitive difficulties with immunologic abnormalities, and found a relationship between certain immune system variables and degree of cognitive disturbance using the Cognitive Difficulties Scale (a self-report behavioural inventory assessing attention, concentration and memory).

3.7 IS THERE A BIOLOGICAL BASIS TO CHRONIC FATIGUE SYNDROME?

Although numerous and diverse attempts have been made to establish a unique biological profile for CFS patients, the results are far from being conclusive. To date, there is evidence of non-specific disordered immunity as well as altered integrity of the CNS and endocrine systems; however, the interdependence of such systems makes it difficult to establish causality. Indeed, Klonoff (1992) points out that "the immune, central nervous system and endocrine systems are functionally intertwined, and endocrine dysfunction may be partly the cause and partly the result of immunologic and neurological dysfunction" (p. 817).

An equally non-specific appraisal of the biological research is given by Demitrack (1994), who, in an attempt to integrate the diversity of biological findings and clinical symptoms, maintains that "in CFS, specific pathological antecedents (e.g. acute infection, stress, pre-existing or concurrent psychiatric illness) may ultimately converge in a final common biological pathway resulting in the clinical syndrome of CFS" (p. 3). Whether or not this indicates that some individuals have a biologically determined propensity for the development of CFS, is not clear, although a genetic predisposition has been suggested by Keller et al. (1994) - see Figure 3-1.

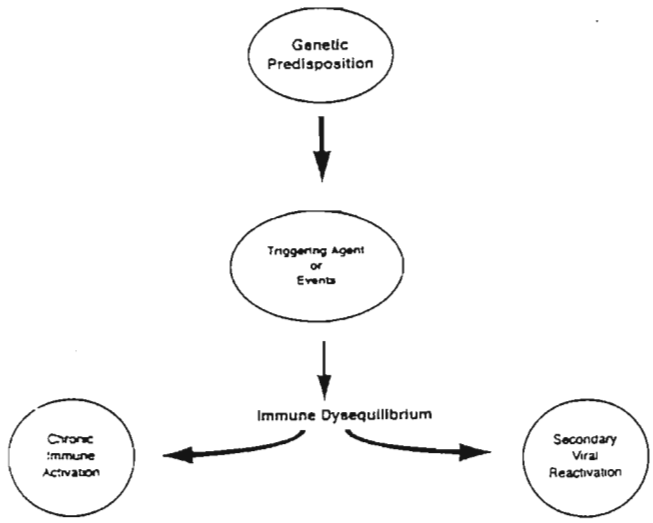

Figure 3-1. Proposed Model for the Pathogenesis of CFS (Keller et al., 1994, p. 156)

In concluding this chapter of the literature review, it would be fair to say that although psychological factors are of considerable importance in the pathogenesis of CFS, a number of findings strengthen the likelihood that CFS is caused primarily by biological factors:

(1) Numerous viruses have been associated with the development and maintenance of CFS symptoms. Although EBV, HHV-6 and Coxsackie viruses are commonly cited precipitants of CFS, they are unlikely to account for all cases (Bearn & Wessely, 1994). Some experts (e.g. Levy, 1994) believe that one virus (not yet identified) is responsible for CFS, but this is not a universally held opinion. Nevertheless, immune system activation is detectable in the majority of cases (manifested as changes in serum levels of cytokines and low numbers of natural killer cells). The pattern of findings appear to support the notion of recovery from viral infection in at least some cases, although a causal relationship between abnormal immune function and CFS is not well-established. Levy suggests that altered immunity may be caused by an undiscovered agent or unknown biological process. There is evidence from the field of immunology that some viruses are able to evade detection by the immune system, thereby avoiding a conventional response or by precipitating subtle changes at the level of muscle physiology or the CNS (i.e. neurochemistry). This, according to some authors (e.g. de la Torre et al., 1991; Wessely, 1993) would explain why routine blood tests often fail to reveal any significant abnormalities in the face of more sophisticated hypothalamic function tests in CFS patients. For some researchers, the heightened immune response has been interpreted as evidence of an autoimmune disease (Twombly, 1994), whereas others such as Bell (1994), suggest that elevated levels of cytokines, particularly those affecting neural tissue, may contribute to the CFS symptom picture.

(2) Alterations in neurotransmitter and neuroendocrine functions are apparent (i.e. HPA dysfunction) although causality is again difficult to establish given that the HPA may be influenced by changes in neurotransmitter function, stress, and immune activation. Nevertheless, pituitary and hypothalamic dysfunction is suspected in at least some cases.

(3) Structural and functional brain changes have been documented in some CFS patients using appropriate investigative techniques (MRI, SPECT etc.), and the limbic system has

been implicated in more than one line of investigation.

The last point is the most relevant to the current study, since such changes question the integrity of normal brain function. If this is the case, deficits in neuropsychological functioning should be apparent using appropriate investigative techniques.

CHAPTER 4

THE NEUROPSYCHOLOGY OF CHRONIC FATIGUE SYNDROME: CURRENT PERSPECTIVES

"Cognitive dysfunction is now regarded as a hallmark of CFS and some well-known clinicians will not make the diagnosis of CFS unless intellectual impairment can be demonstrated" (Goldstein, 1993, p. 46).

Many patients with CFS experience symptoms suggestive of cognitive dysfunction (Wessely & Powell, 1989). The most common cognitive complaints appear to be attentional and concentration difficulties (Hickie et al., 1990), although additional complaints range from forgetfulness and anomia, to difficulties in carrying out complex mental tasks (Altay et al., 1992; Smith, 1991). According to McDonald, Cope, & David (1993), the estimated overall prevalence of subjective cognitive impairment in CFS appears to be in the region of 50-70%. Like the clinical symptoms, some variation in how these experiences might be manifested and experienced are apparent. These symptoms can range from subtle impairment that is barely detectable by the observer or noticed by the sufferer, to profound cognitive debilitation that makes work and recreation difficult. In subtle cases, the individual may easily ascribe the experience of cognitive dysfunction to feeling tired or distracted. The consequences could be potentially devastating; consider the following autobiographical account by a flight surgeon:

> The morning was clear and still as I reported in to the tower at Moffet Field (California). "Cherokee 71 Charlie, report right downwind runway 32 left". I acknowledged what, for 3 years, had been for me a routine entry, and proceeded with the approach. On entering 45 degrees to the correct downwind, I reported "turning *left* downwind for 32 *right* ". The tower operator became appropriately alarmed when she couldn't find me where I said I was, and even more alarmed that I might be doing what I had said. This is when panic struck! I had correctly

> complied, but remained totally confused between *left* and *right*. In fact, I had been having difficulty the whole flight remembering my flight plan and recalling common radio phrases familiar to me for 26 years! Frightened, I managed to continue the pattern toward the runway, but by the time the tower located me , I had lined up on runway 32 *right*, kept open for P-3 traffic, and was halfway down final. She immediately had me manoeuver to 32 *left*, and after landing called me to the base of the tower... I taxied to the ramp, rationalizing the incident as being sleepy. I was aware that I had not been feeling well for several months, but had had no difficulty on other recent flights. That was changing, however, as on my very next flight I again became confused in the pattern. This time I also had trouble with concentration, word recall, and word substitution.
>
> (Harvey, 1989, p. 1199).

At the present time, the cause of CFS-related cognitive dysfunction remains unclear. Some researchers speculate that a subclinical encephalitic process may be involved (Harvey, 1989), whereas others suggest that cognitive dysfunction is associated with major depression (Altay et al., 1992; McDonald, David, et al., 1993) or immune activation (Lutgendorf et al., 1993). Whatever the cause, investigation of the cognitive complaints associated with CFS is of clinical relevance.

One of the issues that becomes apparent when reviewing the literature on cognitive dysfunction associated with CFS, is that these symptoms may be difficult to evaluate and quantify objectively. Some studies have employed self-report questionnaires in an attempt to document the nature and extent of cognitive dysfunction (Berne, 1992; Broadbent et al., 1982; Smith, 1991; Wessely & Powell, 1989). Others (reviewed below) have attempted a more objective evaluation of cognitive difficulties using neuropsychological measures.

Because of their precision and sensitivity to a wide range of neurocognitive variables, neuropsychological tests are ideal instruments for the evaluation of subtle cognitive dysfunction (Lezak, 1983). Despite their suitability, there has been a surprising paucity of neuropsychological studies in the CFS literature until recently. This may, to some extent, reflect a relative shortage

of neuropsychological expertise in many parts of the world, although a more likely explanation may lie in the fact that greater emphasis been placed on the more functional aspects of CFS. In this respect, studies investigating functional conditions such as depression and somatization, appear to have dominated much of the CFS literature until relatively recently. Grafman et al. (1991) have recommended that neuropsychological testing be included in all future studies of CFS; they in fact state that "formal neuropsychological evaluation is the only way of objectively evaluating patient complaints of subtle cognitive deficits" (p. 49).

4.1 NEUROPSYCHOLOGICAL INVESTIGATIONS

As mentioned, the neuropsychological investigation of CFS has gotten off to a slow start. This is especially apparent for the years prior to 1991 (when this research was initiated). Subsequently, there has been a steady trickle of research. Table 4-1 summarizes the representative studies in this area.

One of the first (unpublished) explorations of the cognitive domain of CFS was conducted in 1984 by Estes et al. (as cited in Millon et al., 1989). Unfortunately, their paper was a conference presentation and further information could not be located for this literature review. Nevertheless, Millon and colleagues report that Estes et al. found cognitive deficits in four of their ten subjects. The deficits involved long- and short-term memory (moderate to severe impairment), flexible memory (mild to moderate impairment), fine motor control (moderate impairment), and conceptual learning (severe impairment). In 1989 Bastien published the findings of a neuropsychological investigation in the *CFIDS Chronicle* (as cited in Sandman et al., 1993). Intellectual and memory deficits were found in an unspecified sample of CFS patients; these patients apparently performed below the test norm means on nearly every measure of a 4-hour neuropsychological battery.

Table 4-1. Representative Neuropsychological Investigations of CFS by Tests Used

Author(s)	Tests
Millon et al. (1989)	MMSE, WMS.
Altay et al. (1990)	TMT, WAIS-R (Digit Symbol, Similarities), Shipley Institute of Living Scale.
Daugherty et al. (1991)	Wisconsin Neuropsychological Test Battery (includes WAIS-R, Hand Dynamometer, Tapping Test, Tactual Performance Test).
Smith (1991, 1992), and Smith et al. (1993)	Computerized reaction time measures (simple reaction time, five choice serial response task), *visual sensitivity pattern* (1991 study only), *visual search task*, Stroop colour-word task (unspecified version), *story comprehension and recall*, Digit Span, *word list recall, word recognition task, semantic memory tasks (category and semantic processing).*
Riccio et al. (1992)	National Adult Reading Test (NART), WAIS-R, WMS, Semantic Processing Test, COWAT. Grooved Pegboard, WCST (Nelson modification), TMT.
Grafman et al. (1993)	WAIS-R, simple reaction time, serial reaction time test, *time wall* (computerized perceptual reaction time task), time clock (time estimation task), Tower of Hanoi, Twenty Questions (deductive reasoning task), WMS-R, *experimental paired association test. Hasher frequency monitoring task, story memory*, COWAT.
McDonald et al. (1993)	Quantitative Neurological Examination (QNE), Serial 7's, Star Cancellation Test, WMS (Digit Span and Paired Associates).
DeLuca, et al. (1993)	PASAT, WAIS-R (Digit Span, Vocabulary, Similarities).
Sandman et al. (1993)	MMSE, WMS-R, Wisconsin Card Sorting Test, TMT, Boston Naming Test, LNNB (Visual-Function scale), Irvine Memory Battery (computer administered).
Ray, Phillips, and Weir, (1993)	Everyday Attention Questionnaire, Profile of Fatigue-Related Symptoms, Stroop Colour-Word Interference Test, Embedded Figures Test.
Schmaling et al. (1994)	Stroop Test, Short Category Test (Booklet Form), CVLT, WMS-R (Visual Memory Span, Visual Reproduction), WAIS-R (Vocabulary, Block Design, Digit Span, Digit Symbol), WCST, Dot Counting Test, Rey's 15 Item Test.

Table 4-1 (continued). Representative Neuropsychological Investigations of CFS by Tests Used

Author(s)	Tests
Krupp et al. (1994)	WAIS-R (Information, Vocabulary, Block Design, Object Assembly, Digit Span, Digit Symbol), Selective Reminding Test, WMS-R (Logical Memory, Paired Associates), BVRT, COWAT, Finger Oscillation Test, SDMT, Booklet Category Test, WRAT -R.
Johnson et al. (1994)	CVLT.,
De Luca et al. (1995)	WAIS-R (Digit Span), PASAT, Booklet Category Test, CVLT, WMS-R (Logical Memory), Rey Complex Figure.
Cope et al. (1995)	NART, WAIS-R (Vocabulary, Comprehension, Similarities, Block Design, Object Assembly), WMS-R, Warrington Recognition Memory Test (*including self assessment modification*), Graded Naming Test, *word stem completion (test of implicit memory)*, supraspan word list (15 common household objects), COWAT, *speed of information processing* (an index derived from the time taken for the first six items of Block Design, and first three items of the Object Assembly test).
Michiels et al. (1996)	WAIS-R (Vocabulary , Digit Symbol, and Digit Span), Finger Tapping Test, Selective Reminding Test, Memory for Location Test, TMT, Ravens Progressive Matrices.
Marshall et al. (1996)	Continuous Performance Test (Identical Pairs version)
Bastien et al. (1996)	WAIS-R
Marshall et al. (1997)	Stroop Test, Buschke Selective Reminding Test, Continuous Performance Test- Identical Pairs Version, PASAT, Simple and Choice Reaction Time Tests, Salthouse Reading Span Test, Verbal Scholastic Aptitude Test.

Abbreviations: BVRT = Benton Visual Retention Test, COWAT = Controlled Oral Word Association Test, CVLT = California Verbal Learning Test, LNNB = Luria-Nebraska Neuropsychological Battery, MMSE = Mini Mental State Examination, PASAT = Paced Auditory Serial Addition Task, SDMT = Symbol Digit Modalities Test, TMT = Trail Making Test, WAIS-R = Wechsler Adult Intelligence Scale - Revised, WCST = Wisconsin Card Sorting Test, WMS and WMS-R (Wechsler Memory Scale and Wechsler Memory Scale - Revised), WRAT-R = Wide Range Achievement Test (Revised). Note: Lesser-known "in-house" measures appear in italics.

In terms of formal publication, Millon et al. (1989) can be credited as being the first researchers to venture into the neuropsychological domain of CFS. Although essentially an investigation of psychological factors (see Table 2-1, p.83), these investigators administered the Wechsler Memory Scale (WMS) as part of a wider psychometric evaluation of 28 patients with CFS. Significant differences between the CFS patients and existing published norms were found for all but one of the WMS subtests (*Logical Memory*). Apart from the recognition of the limitations of the WMS mentioned by these investigators, interpretation of this finding is difficult owing to the use of outdated WMS norms.

In the Nevada CFS outbreak Daugherty et al. (1991) assessed 19 patients using a range of cognitive measures (see Table 4-1). Results revealed significant dysfunction in the areas of attention-concentration, problem solving, motor speed, and verbal memory. MRI scan abnormalities were also found in this study, although the relationship between these and the cognitive deficits was unfortunately not reported. Smith (1991, 1992) and Smith et al. (1993) have published a series of studies investigating the behavioural and cognitive aspects of CFS. In the first of these, 232 ME patients were contrasted with 100 healthy controls on the Cognitive Failures Questionnaire (CFQ). Results indicated a greater degree of cognitive failure (e.g. concentration and memory problems) in the CFS group. Tests of cognitive functioning were subsequently administered to a subset of these individuals (18 CFS patients and 9 controls); the CFS patients were found to be slower at psychomotor tasks (simple reaction time, five-choice serial response task) and experienced problems with selective and sustained attention (letter cancellation, Stroop test). Selective memory deficits (e.g. poor story recall) and increased sensitivity to visually disturbing patterns were also found. Intact functioning was however evident on measures of digit span, word recall and recognition memory. One criticism of this particular study lies in the selection of the neurocognitive measures, since many of the tasks were "in-house" computer-administered tasks not routinely used in clinical practice or available to other investigators. The reliability of the cognitive deficits found in the initial study was investigated in a follow-up study, this time using a test-retest design. Eight CFS subjects and twenty-three healthy controls were assessed using a range of tasks assessing motor speed, attention, logical reasoning, and semantic memory. The CFS group performed these tasks more slowly and less accurately. This group difference was found to be stable over time (six months).

The initial (i.e. 1991) investigation was extended geographically to Glasgow (Scotland) where 57 CFS patients were studied together with 19 matched controls (Smith, 1992; Smith et al., 1993). Questionnaire assessment of the more psychological and somatic symptoms indicated that the CFS group reported higher levels of depression, anxiety, physical symptoms and cognitive failures. Significant group differences were again evident for almost all of the neurocognitive tasks (only *Digit Span* and a free recall memory task failed to discriminate between the groups). None of the performance differences could be attributed to depression.

Riccio et al. (1992) reported generally normal neuropsychological profiles in nine CFS patients (mostly with EBV) who were compared with a carefully matched control group (i.e. matched on age, sex, education and premorbid intelligence). Apart from the neuropsychometric tests, a series of self-report psychological questionnaires (Present State Examination, Hospital Anxiety and Depression Questionnaire, State-Trait Anxiety Inventory, Profile of Mood States, Illness Behaviour Questionnaire and the Eysenck Personality Questionnaire) were also administered. Only 2 of the 15 neuropsychological test scores revealed a significant group difference: *Logical Memory* (a measure of short-term recall) and *Associate Learning* (a measure of verbal learning). Riccio and colleagues expressed surprise that the tests they had anticipated would be most likely to reflect the clinical complaints of psychomotor slowing and fatigue (i.e. Grooved Pegboard and Trail Making Test), failed to differentiate the CFS and control groups. However, it is possible that statistical power was lost because of the very small sample used.

Other studies have failed to find evidence of neuropsychological impairment. Altay et al. (1990) assessed 21 CFS patients using a test battery comprised of two subtests of the WAIS (*Digit Symbol* and *Similarities*), the Trail Making Test and the Shipley Institute of Living Scale (a measure of intellectual functioning and cognitive deterioration). Results showed significantly *superior* performance in the CFS group on all but one of the measures (Trails A). In addition, these authors reported an interesting discrepancy between perceived cognitive difficulty and actual test performance (i.e. the CFS patients felt that they had performed more poorly than their test scores indicated). However, methodological problems with this study are apparent. No control group was employed (the test results were compared to age-matched normative groups). Sample bias is therefore apparent if one considers the generally high educational, occupational,

and social status of the participants of this study. A further criticism of this study lies in the selection of neuropsychological tests in that no tests of memory or learning (i.e. areas of known impairment in CFS) were included.

Studies conducted over the past three to four years have attempted to remedy some of the limitations of the earlier investigations. In a pilot survey using questionnaire measures, Grafman et al. (1993) found a consistent correlation between the severity of mood disturbance (depression) and the number and severity of memory complaints in CFS patients ($N = 54$). This formed the basis for a more complete analysis of neurocognitive functioning, and they compared the performance of 20 CFS patients with 17 age- and education-matched healthy controls on a comprehensive battery of neuropsychological measures assessing memory, planning, reaction time, intelligence, and time perception. In addition, four screening measures of psychiatric and somatic functioning were administered. Normal and occasionally superior performance was found for individuals in the CFS group for all of the neuropsychological measures with the exception of two memory tests. These were the global memory index (MQ) of the Wechsler Memory Scale (the deficit was mainly attributable to selective impairment on the visual reproduction subtest in which the subject is required to recall complex geometric designs), and secondly, cued recall on the experimental paired associates task. This latter finding of significantly worse performance on cued as opposed to free recall is noteworthy because it is opposite to what might be expected in both normals and most organic brain conditions. This paradoxical finding could not be satisfactorily explained by Grafman et al., although they felt that because VIQ was significantly correlated with memory performance, that an overall decrement in general verbal skill may have contributed to the pattern of results. A number of criticisms can be directed at this study. Firstly, only normal controls were used. Secondly, the patient group was highly selected and may not have represented a demographically diverse group. Thirdly, although a broad range of neuropsychological measures were employed, a lack of validation studies on some of the measures makes interpretation of the results problematic.

McDonald et al. (1993) administered a brief screening battery of neuropsychological tests to 65 CFS patients randomly selected from a large group of general practice attenders ($N = 686$). In addition to the cognitive measures, the Clinical Interview Schedule (CIS-R) was also

administered as a measure of minor psychiatric disorder. Neuropsychological impairment was detected in 25% of the CFS patients on two of these measures (serial 7's and star cancellation), leading the authors to conclude that subjectively reported attentional difficulties and memory disturbance in CFS can be objectively validated. One finding of this particular study was that despite experiencing initial difficulty on some of these tasks, the more chronically fatigued CFS patients were able to "catch up" to their less fatigued counterparts over successive trials. Like the study of Grafman et al. (1993), the nature of the memory impairment was interpreted as a being somewhat different to that seen in severely depressed and amnesic patients.

The quality of attention in CFS patients was investigated by Ray et al. (1993) using two self-report measures (Everyday Attention Questionnaire, Profile of Fatigue-Related Symptoms) and two tasks requiring focussed attention (Embedded Figures Test, Stroop). The study sample comprised 24 CFS subjects (16 female and 8 male); these were compared to gender-matched healthy controls of similar (but not matched) ages. Group differences were apparent on the subjective questionnaires as well as on the *Word* and *Colour* scores of the Stroop measure. Positive correlations were found between these scores and the emotional distress/somatic symptoms of the Profile of Fatigue-Related Symptoms questionnaire, although in general, there was a lack of association between subjectively-rated attentional deficits and performance on the objective attentional measures. The authors attributed this to the disparity between the various measures used, as well as to poor ecological validity of the formal tests.

Seeking to address the shortage of studies using control groups, DeLuca et al. (1993) compared 12 female CFS patients with age-, education-, and verbal intelligence-matched controls (an MS group consisting of 11 patients diagnosed with multiple sclerosis[40] and 11 healthy volunteers; the control groups consisted of 10 females and 1 male respectively). Group differences emerged for the PASAT (the performance of the CFS and MS groups was significantly poorer than healthy controls) and Digit Span, where the CFS patients differed from both control groups. These deficits could not be attributed to depression. The authors concluded

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Justification for the use of MS patients as comparison groups in CFS studies comes from neuropsychological findings of impaired information processing efficiency, learning and memory, as well as a high incidence of fatigue and depression in these patients (DeLuca et al., 1993).

that both CFS and MS patients demonstrate impaired information processing efficiency, a finding which they felt could explain other cognitive complaints reported by CFS patients. This conclusion would be consistent with current conceptual models of neurocognitive functioning (e.g. Reitan, 1988) which indicate that higher cognitive functions are critically dependent on intact attentional processes.

Sandman et al. (1993) also used a case-control design in their study of 39 CFS patients, this time employing DSM-III-R diagnosed depressed patients along with normal volunteers (n = 23 and n = 129 respectively). They found generally normal neuropsychological profiles (test scores comparable with published norms) although on the computer administered memory tasks, a number of difficulties characterized the CFS group. For example, they tended to overestimate their ability (metamemory), performed worse on tests of recall as context increased (e.g. recognition memory), made more errors when rehearsal was prevented, and exhibited delayed mental scanning as memory load increased. The authors offered a memory consolidation or stimulus registration deficit as an explanation. Clinically speaking, these findings suggest an overall fragility of memory processes and are similar to the types of deficits seen in axial amnesias (i.e. pattern of weak consolidation and vulnerability to interference). Interestingly, the unusual finding of impaired recognition memory parallelled the findings of Grafman et al. (1993) and McDonald et al. (1993).

The research team of DeLuca and colleagues (i.e. Johnson et al., 1994), turned to the California Verbal Learning Test (CVLT) in an attempt to unravel the nature of the memory impairment reported by others. This measure appears to be gaining increasing popularity as an alternative to the more widely used Auditory-Verbal Learning Test; both offer an opportunity to sample rate of learning, retention, effects of interference and recognition memory. In this study, 22 CFS patients were contrasted with 21 age- and education-matched healthy controls. The absence of any group differences on the CVLT led these authors to conclude that there is no primary verbal memory impairment in CFS, but that reported cognitive difficulties are related to deficient information processing (especially memory encoding), rather than impaired storage and/or retrieval of verbal information. They suggested that future studies need to focus on attention and concentration as components of this faulty processing.

Schmaling et al. (1994) also used the CVLT together with other neurocognitive measures of memory and information processing (e.g. Stroop, Trail Making Test). Sixteen CFS patients were contrasted with twenty-three depressed patients. No group differences emerged on any of the measures used, and the authors noted that both groups scored within normal limits on most measures. Test-score variability was found to be unrelated to the level of depressive symptoms. Subjective ratings of fatigue taken before, during, and after the test procedures revealed that the CFS group perceived themselves to be more fatigued than controls at every point of assessment.

An extensive neuropsychological battery was administered to 20 CFS patients and control groups of 20 healthy individuals and 20 MS (multiple sclerosis) patients in a well-controlled study by Krupp et al. (1994). All three groups were matched on tests of premorbid ability (WAIS-R and WRAT-R). In general, the MS group performed less well than the other groups on the neuropsychological measures (listed in Table 4-1). Compared to healthy controls, the CFS patients attained a significantly lower test score on only one measure (*Digit Symbol*) although all tests exhibited a trend towards weakened performance. Based on neuropsychological ratings of impairment, 35% of the CFS patients were regarded as cognitively impaired (compared with 60% of MS patients and 5% of healthy controls). In contrast to these findings, the MS group revealed greater relative impairment to healthy controls (five of nine neuropsychological measures). Depression was found not to contribute to cognitive deficits in either the CFS or MS groups. Krupp and colleagues concluded that cognitive dysfunction is more extensive and severe in MS than in CFS patients.

A similar study, but with an added control group of depressed patients, is reported by DeLuca et al. (1995). The CFS group of 26 patients was compared to age-, sex- and education-matched controls comprising 12 MS patients, 14 depressed patients and 20 healthy controls. Subjectively-rated cognitive impairment was most prominent for the CFS group, although all three clinical groups showed increased complaints of memory relative to controls. The CFS group performed worse than the three control groups on the PASAT, while the MS and depressed groups did not differ statistically from the healthy controls. PASAT performance was not affected by either anxiety (State Trait Anxiety Inventory) or depression (Beck Depression Inventory); see also Table 2-1. For the memory tests, only the MS group recalled fewer elements

on the *Logical Memory* passage of the Wechsler Memory Scale. However, this finding was due to a deficit in the initial acquisition of the material; no group differences were apparent when this was partialled out. Difficulty in the acquisition of new verbal material (CVLT) was reflected in the poorer CFS cumulative total of the five learning trials, while long term recall was also worse than the other groups (immediate and delayed free recall conditions). There were no group differences in terms of cued recall or recognition memory, and overall, the MS group did not differ from healthy controls on the CVLT measures of acquisition, recall or recognition. An impairment rating (based on *SD*s from the mean performance of the healthy controls) was computed and revealed significant group differences (CFS and depressed patients performed worse than controls in terms of overall neuropsychological performance). De Luca et al. recommended that closer attention be paid to the nature of the attentional disorder in CFS since they felt that this could explain the subtle memory difficulties reported by themselves and others. Specifically, they hypothesized that rather than being due to a deficit in storage, consolidation, or retrieval of the memory trace, a reduced ability to process auditory information was responsible for the observed findings.

Cope et al. (1995) used an extensive neuropsychological battery to study three groups: a CFS group ($n = 26$); a control group of age-matched healthy individuals ($n = 18$); and a further control group ($n = 13$) comprised of age-matched depressed patients (ICD-10 diagnosis). Additional measures included the BDI and MRI scanning (see reference to latter findings in Chapters 2 and 3). General cognitive functions (as measured by the WAIS-R and NART) as well as WMS-R performance, failed to show any group differences (with the exception of lower *Object Assembly* in the depressed patients). The Graded Naming Test was also completed adequately by all three groups. The speed of information processing tasks revealed two differences: depressed subjects took longer on the mental control task and the WAIS-R *Object Assembly* subtest than the control groups. In a unique extension of the research in this area, the authors conducted an incomplete follow-up assessment three to six months later on 14 of the CFS patients. They found improved scores on the *Block Design*, supraspan and hard verbal *Paired Associates*. In addition, there was reported improvement in fatigue levels. Since a control group was not tested, it is difficult to ascertain whether the improved performance represents a true improvement or whether it was due to a practice effect. Subjective complaints of cognitive

complaint were also evaluated by Cope et al. (1995); they found a strong positive correlation between this and measures of depression, anxiety and fatigue. In addition, they found that with the exception of one test (*Visual Memory* - WMS-R) there was no relationship between objective test performance and subjective cognitive complaint (i.e. those who reported significant difficulty performed as well as those with few complaints). The authors concluded that there were no conspicuous neurocognitive differences between CFS patients and matched controls, and that on the basis of their data, it was unlikely that CFS was a post-encephalitic condition.

The possibility of IQ changes in CFS was investigated by Bastien et al. (1996). The Wechsler Adult Intelligence Scale, Revised (WAIS-R) was administered to 72 CFS patients (repeat testing was performed on at least one other occasion during the course of their illness). The follow-up IQ testing revealed a significant decline in the CFS group (average change was 13.3 points with a range of 0-43). The apparent cognitive decline was maximal for the subtests making up the PIQ index and arithmetic ability. It is difficult to know how to interpret this study given that no controls were employed, the test-retest period is not specified, and also the fact that improved IQ on retesting was frequently seen.

Michiels et al. (1996) evaluated 35 CFS patients and 33 matched controls (age, gender, intelligence and education) using a range of neuropsychological measures (see Table 4-1). Results of MANOVA revealed significant impairment of subjects with CFS in comparison to normal controls on tasks of verbal learning/memory (Selective Reminding Test), attention/ concentration (*Digit Span, Digit Symbol*) and fine motor speed (Finger Tapping Test). In contrast to other studies there was no indication that a higher level of depression (as measured by the Beck Depression Scale) resulted in lower test performance in the CFS group; in this regard, the highest correlation (.32) was found with Part A of the Trail Making Test. Stepwise discriminant analysis showed that an 85% correct classification could be made on the basis of four measures (SRT delayed recall and total long term store, finger tapping, and digits forwards). With regard to the memory measures, patients with CFS learned at a lower rate that did normal controls. The authors concluded that "the nature of the memory problems reflect attentional deficits that, in turn, support the notion of general slowing of information processing, and impaired effortful

cognitive processing"[41] (p. 673).

As part of an investigation into allergy treatment in CFS patients, Marshall et al. (1996) administered the Continuous Performance Test (CPT) to 27 CFS patients and compared their performance with that of 10 unmatched depressed allergy patients and 8 healthy controls. Results failed to indicate a statistical difference between the groups on a measure of sustained attention; in addition, when compared with normative data, the performance of the CFS patients fell within normal limits. However, an attentional dissociation between the verbal and figural stimuli used as distractors in the CPT revealed a group difference. Specifically, the depressed individuals had greater difficulty attending to figural stimuli as opposed to verbal stimuli than the other groups. This dissociation was not evident for the CFS patients whose performance closely resembled that of the healthy controls.

The most recent study found for inclusion in this section of the literature review, is one by Marshall et al. (1997). The design was similar to the current study; 20 CFS patients were compared with 20 healthy controls and 14 patients with a history of major depression or dysthymia. Matching was made on the basis of age, intelligence, education, and sex, and each study participant completed a test battery comprised of six measures (see Table 4-1). Given the common complaint from CFS patients that they can competently complete challenging tasks on one day, but typically feel exhausted and fatigued the next, these investigators incorporated a two-day testing procedure in their design. In addition to the test procedures on the first day, they also had their subjects walk for 30 minutes on a treadmill to increase fatigue levels after testing. Contrary to the claims of post-exertional fatigue by CFS patients, results indicated that CFS patients did not exhibit a decline in performance from one day to the next. In terms of the neuropsychological variables, the CFS patients performed below the control groups on three of the seven measures (PASAT, Stroop, and Reaction Time Tests). All of these measures are sensitive to speed of cognitive processing, an ability which the authors suggest is compromised

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[41] The distinction between effortful and automatic processing is considered to be consistent with models of memory that distinguish between an intentional, conceptually driven, elaboration process (referred to as explicit memory), and a more automatic, data-driven activation process, known as implicit memory (King & Caine, 1996). In the former, the subject is conscious of what is being tested, whereas implicit memory tasks do not necessarily involve awareness (i.e. there is unconscious activation).

in CFS patients. In terms of the magnitude of difficulty, the CFS group were found to perform about 1 *SD* below the control groups' performances, a discrepancy which some researchers accept as evidence of clinical impairment. Owing to nature of the reported depression (i.e. secondary versus primary) in the CFS group, the authors were unable to say whether depression per se has an influence on cognitive slowing; on the other hand, they felt that a reactive depression could account in part for the test performance in the CFS group.

4.2 NEUROPSYCHOLOGY OF DEPRESSION

The possibility that cognitive dysfunction in CFS may in part be attributable to depressive symptomatology has been alluded to in some but not all studies reviewed above. That severe depression can result in memory deficit is well established in the psychiatric and neuropsychological literature (King & Caine, 1996; Massman et al., 1992; Watts, 1995) and is not debated here. Newman and Sweet (1992) and Watt (1995) provide useful reviews of findings in this area and these are summarized in Table 4-2. The effects are sufficiently precise so as to allow for a consistent profile of reasonably intact encoding and storage of material, poorer retrieval, but relatively normal recognition memory in depressed patients (Massman et al., 1992). In addition, depressed patients make few intrusion errors and retain over long periods, most of the information they had managed to learn initially (ibid). Watts (1995) suggests that depressed subjects do not necessarily present with a memory capacity problem per se, rather their performance is impaired owing to a failure to spontaneously adopt optimal processing strategies. Unfortunately, the impact of various subtypes of depression (e.g. primary versus secondary) on neuropsychological test performance has not yet been systematically investigated. In addition, King and Caine (1996) point out that subject variables such as severity of depression and/or hospitalization are important determinants of the degree of impairment.

Table 4-2. Neuropsychological Correlates of Depression

Psychomotor retardation:	slowed motor and mental functioning are consistent findings and may be manifested in slowed performance on measures like the Trail Making Test.
Motivational attentional deficits:	a tendency to negatively self-evaluate and to fail tests by employing more conservative response strategies have been found. Depressed individuals do poorly on tasks requiring increasing levels of sustained effort and concentration, and tend to perform better on minimally demanding tasks.
Memory and learning:	compared to normals and organic patients, the test performance of depressed individuals is characterized by the following: (1) *incidental versus intentional learning* - incidental learning is usually better in depressives than in organic patients; possibly due to the fact that it is a relatively effortless task. (2) *recognition versus recall* - while normal individuals usually perform equally well on recall and recognition tests, depressed patients show a pattern of intact recognition but poor recall; this may be due to poor organization of traces, since increased structure has been found to lead to improved performance. (3) *easy versus hard paired associate learning* - although normals, depressives, and Korsakoff's patients perform equally well on learning easy word pairs, performance on learning hard associates discriminates normals from the other two groups. For the depressed patients performance declines in the face of effortful processing (i.e. when they are required to impose their own strategies for learning unrelated words). (4) *recall for related versus unrelated word lists* - comparisons between organic (demented) and depressed patients reveals the fact that depressed individuals do better at remembering semantically related word lists (e.g. words within a particular category) than lists of unrelated words. The explanation offered is the same as in (3) and implies that depressive but not organic patients, can make better use of cognitive organizational strategies to facilitate recall.

(Newman & Sweet, 1992; Watts, 1995).

The attentional deficits which characterize depression also appear to be different from those that characterise CFS. As mentioned, McDonald et al. (1993) commented that their subjects appeared to manifest some recovery of ability. This pattern is opposite to what might be expected in depression, where subjects may be predisposed to give up easily and show a performance decrement over time. Unfortunately, many of the studies reviewed above have been limited in their assessment of attentional and memory functions, and this has restricted the conclusions that may be drawn. It would also seem important for studies to attempt to link CFS-induced cognitive difficulty with psychological states (e.g. depression) and cognitive processing strategies. This can only be achieved through careful selection of neuropsychological instruments.

4.3 CONCLUSIONS

What conclusions can be reached on the basis of the neuropsychological studies reviewed above? Certainly, while there is little support for gross neurocognitive impairment in CFS, there is some support for the idea of memory inefficiency and other forms of information processing deficits; however, the precise mechanism underlying these problems is currently unknown. A deficit in the processing of complex auditory information (i.e. auditory attention) has been hypothesized by DeLuca et al. (1993), although this has generally not been supported by studies employing digit span as a measure of auditory attention (e.g. Smith et al., 1993; Grafman et al., 1993). A deficit in actual attentional capacity (as opposed to selective attention, response selection, and sustained attention) in CFS patients has been proposed by Marshall et al. (1997); this point is taken up again in Chapter 8 (Discussion). Some appeal has been made for future studies to use appropriate control groups and employ a wider range of information processing tests (Schmaling et al., 1994; DeLuca et al., 1995). In addition, Schmaling et al. make the observation that few studies have attempted to describe results in terms of absolute performance values. In this respect, there has been a tendency (e.g. Riccio et al., 1992) to describe group differences in terms of impaired neurocognitive competence, even when test scores fall within the normal range. From a methodological standpoint, uniformity of statistical analyses would also greatly facilitate inter-study comparisons.

Two other reasonably consistent findings are worth mentioning here. Firstly, the nature of the reported memory difficulties in some of the CFS studies is somewhat atypical of organic amnestic disorders. Specifically, impaired recognition memory in the face of intact free recall is an unusual feature, although it may be related to the impaired information processing mentioned above. Secondly, a number of studies have remarked on the dissociation between subjective and objective neurocognitive complaints (Altay et al., 1990; Cope et al., 1995; DeLuca et al., 1995; Ray et al., 1993). The tendency to underestimate one's ability is not unique to CFS since this has also been documented in depression (Newman & Sweet, 1992; Watts, 1995). One can only speculate on the underlying mechanisms, although it seems reasonable to suggest that in a highly somatically experienced condition such as CFS, there may be a tendency on the part of the sufferer to focus on, and even magnify relatively minor cognitive complaints. On the other hand, activation of the immune system with subsequent release of cytokines could give rise to subtle cognitive deficits that may not always be apparent on testing.[42] Interestingly, and as mentioned above, McDonald et al. (1993) found that their patients were able to overcome apparent fatigue and improve their performance over time; a tendency which has also been observed in patients with severe depression (ibid). According to Wessely (1993), depressed patients experience difficulties with effortful processing.

The subcortical dysfunction hypothesis has been proposed as an etiological explanation for memory deficits related to both CFS and depression (Bruno et al. 1996; King & Caine, 1996; Massman et al, 1992). This hypothesis suggests that the nature of the memory impairment seen in depression and CFS, closely resembles that seen in patients with subcortical or basal ganglia dysfunction. Specifically, depressives and patients with subcortical neuropathology appear to have problems in memory retrieval. Goldstein (1993) provides a more direct link with CFS when he suggests that CFS may be conceptualised as a "dysregulation of the hippocampal neural network" (p. 27). This involvement of the limbic system as an explanation for CFS-induced memory deficit would be fully compatible with the generally accepted view that CFS involves

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[42] Subtle neurocognitive dysfunction may not be readily identifiable on routine neuropsychological testing. Firstly, it is possible that the novelty and artificial setting of the testing environment is sufficient to prime the testee to perform at above regular ability due to increased arousal (Lezak, 1995). Secondly, it is possible that many forms of neuropsychological examinations are either too insensitive, or too short to precipitate fatigability and lower the threshold against which defective performance might be seen.

dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.

Notwithstanding the methodological weaknesses in the neuropsychological investigation of CFS, a further difficulty becomes apparent at the level of interpretation of psychometric findings. For example, Riccio et al. (1992) suggest that their findings "point to the presence of an organic, probably viral, etiology" (p. 118). Wessely (1993) is of the opinion that this kind of interpretation is problematic given the range of variables that can affect neuropsychological test performance and the fact that neuropsychological tests cannot be independently used to determine etiology. Similarly, Cope and her colleagues say:

> we are critical of what we regard as the misuse of neuropsychological test results to confirm or refute an organic basis for the CFS. The absence of neuropsychological deficits in our sample does not make their subjective complaints any less real (Cope et al., 1995, p. 93).

Problems related to the generalization of neuropsychological findings are mentioned by Michiels et al. (1996). Specifically, they feel that the high intra-group variability in test scores and cognitive dysfunction limits the applicability of their and other study findings, to the entire CFS population. Their observation obviously calls for greater effort in ensuring CFS group homogeneity.

In conclusion, a paucity of research employing appropriate (i.e. conceptually-driven) test batteries and adequate controls, characterises the neuropsychological investigation of CFS. This is also recognized by Wessely (1993) who states that "future studies must be based on a better understanding of the nature of the deficits that might underlie CFS, and fewer 'fishing exercises' testing anything and everything" (p. 218).

CHAPTER 5

THE NEUROPSYCHOLOGICAL PARADIGM AND STATEMENT OF AIM

5.1 ISSUES IN THE CURRENT PRACTICE OF NEUROPSYCHOLOGY

The purpose of a neuropsychological assessment, as defined by Benton (1994), is "to draw inferences about the structural and functional characteristics of a person's brain by evaluating an individual's behaviour in defined stimulus-response situations"(p. 1). In contrast to naturalistic or clinical observations which characterize much of neurology, these stimulus-response situations are operationalised as psychometric procedures (i.e. neuropsychological tests). However, it should be pointed out that a number of limitations characterize the neuropsychological paradigm. Perhaps the main one is that in contrast to other forms of psychometric assessment, neuropsychological testing has been described as "a mere cottage industry, lagging far behind educational or personnel testing in measurement precision, sophistication, and technology use" (Retzlaff & Gibertini, 1994, p. 186). Their important observation relates not only to the lack of information on the psychometric properties of various commonly used measures, but also to broader conceptual issues as they relate to reliability and validity of neuropsychological testing. A further drawback of neuropsychological tests is the shortage of normative data, and it is not uncommon to encounter published research that has relied on very small stratified samples. One of the challenges facing neuropsychology is for researchers to generate adequate normative data for evaluation and comparison purposes. A fairly recent trend in the neuropsychological literature has been the appearance of demographically-corrected normative data bases (e.g. Tuokka & Woodward, 1996). However, this laudable effort is still problematic; Axelrod and Goldman (1996) point out that standard scores can give misleading impressions if the assumption is made that different measures are directly comparable (i.e. the explicit demographics from which the standard scores are derived are not always comparable). Despite these psychometric limitations, neuropsychological assessment appears to have sufficient discriminative validity to enable it to remain not only a legitimate, but also a valuable and cost-effective assessment resource.

The practice of clinical neuropsychology involves the administration of various tests which will hopefully cover a representative set of cognitive functions, or will at least have sufficient breadth to answer the referral question. Typical areas of function covered by a comprehensive neuropsychological assessment (with representative tests) are summarized in Table 5-1. While this represents a battery for general use, tests may be substituted, added or subtracted, depending on the purpose of assessment. For instance, the assessment of multiple sclerosis, epilepsy, and mental efficiency may necessitate the construction of a modified test battery (see Lezak, 1995; pp. 122-124 for recommendations in this regard). Similarly, the National Institute of Mental Health in the USA have made recommendations with respect to test batteries suitable for the assessment of HIV infection and AIDS (Butters et al., 1990). Likewise, when following a research protocol, test selection and battery construction will be informed by measures which will test the hypothesis under investigation.

Although the construction of an appropriate battery requires some degree of neuropsychological expertise, the real challenge for the neuropsychologist lies within the realm of interpretation. Benton (1994) points out that one misconception is that neuropsychological assessment is comparable in nature to more specialized neurological techniques (e.g. CTscan, and EEG). Not only does neuropsychological assessment have at least equivalent or better diagnostic power to these measures of brain function, it also provides a different kind of data based on clinical-behavioural information. As such, a number of intrinsic and extrinsic factors may influence test performance; this situation creates a challenge for even the most skilled neuropsychologists since he or she is required not only to partial out the effects of various factors on the assessment results, but also to make a meaningful integration of qualitative and quantitative data. Pitfalls of neuropsychological interpretation include: problems of construct validity and overgeneralizing; the risk of over- or under-interpretation; problems of false negatives; confirmatory bias; redundancy of test procedures due to high inter-correlation; and under-utilization of base rates (Benton, 1994; Crosson, 1994; Lezak, 1995; Miller, 1992; Walsh, 1992). Unfortunately, it seems that experience in the field does not immunize one against the problems associated with clinical judgement in neuropsychology; as a consequence, there have been calls for clinicians to make greater use of actuarial methods in neuropsychological decision-making (Faust et al., 1988; Wedding & Faust, 1989).

Table 5-1. Areas of Neuropsychological Function and Representative Tests in a Typical Test Battery

(1) Attention and concentration:	Digit Span and Arithmetic (WAIS), Symbol Digit Modalities Test, Trail Making Test, Stroop Test, Paced Auditory Serial Addition Test.
(2) Memory and new learning:	Wechsler Memory Scale, Sentence Repetition Test, Auditory Verbal Learning Test, a visual recognition test (various options), delayed recall/incidental learning (story recall, Rey Complex Figure, recall of Symbol Digit pairings).
(3) Verbal functions/academic skill:	Comprehension, Similarities (WAIS), naming test (such as Boston or Graded), Controlled Oral Word Association Test, Wide Range Achievement Test, Token Test, Aphasia Screening Test.
(4) Visuospatial functions:	Block Design and Object Assembly (WAIS), Complex Figure Test, drawing tasks, 3-D design reconstruction, Hooper Visual Organization Test.
(5) Executive functions:	Category Test, Wisconsin Card Sorting Test, Colour-Form Sorting Test (Weigl), Austin Maze, Tower of London, Controlled Oral Word Association Test (Verbal Fluency),
(6) Motor/sensory functions:	Revised Quick Neurological Screening Test, Graphasthesia Test (number writing), Single and Double Simultaneous Stimulation Test, Grip Strength, Grooved Pegboard, Finger Tapping Test, Tactual Performance Test, Tactile Form Recognition Test.
(7) Psychological functions:	Symptom Check List-90-R, Cognitive Failures Questionnaire.

The process of test interpretation for research-oriented neuropsychologists may be equally daunting and pitfalls may range from problems of statistical inference using multiple measures (Egan, 1992), to distribution problems (Russell, 1994). Although the statistical comparison of experimental and control group means appears to be standard practice for detecting impairment

in neuropsychological research, this procedure can be problematic. For instance, Butters et al. (1990) argue that a deceptive picture may emerge when the normal performances of healthy individuals mask the impaired scores of dysfunctional individuals; in short, group mean comparisons may not allow one to detect subtle deficits on a neuropsychological test battery. Similar reservations about the limitations of grouped data are expressed by Phillips and McGlone (1995). At the opposite end of the interpretative spectrum is the tendency to equate statistically significant group differences with clinically significant abnormalities in neuropsychological function. Both types of problems can be overcome by converting raw test scores into standard scores. The rationale is that raw test scores are of limited diagnostic value in clinical neuropsychology because they are not informative about how an individual has performed on a particular test. To better understand the diagnostic significance of an individual test score, it has to be compared to a relevant normative population (i.e. it involves computing a standard score). Lezak (1983) reports that most test-makers report test scores as scaled scores (usually a *T*-score or percentile) in which direct comparisons of individual performance to the normative data base can be made. However, this situation holds true only for only a limited number of tests and many clinical neuropsychologists who assemble their own test batteries will be faced with having to compare disparate test scores. To get around this difficulty it is common clinical and research practice to compute a standard score which allows inter-test and inter-group comparisons; the standard score most commonly used in these circumstances is the *z*-score (a measure of the extent to which a score deviates from a population mean). Although Lezak (1983) endorses the view that *z*-scores are an appropriate way of analysing neuropsychological test data, she cautions that meaningful interpretations can only be made when the standardization populations of the various tests have similar demographic distributions. Similar reservations about *z*-score usage are also expressed by Russell (1994) who suggests that a high degree of inter-test variability (in terms of distribution characteristics) exists for most neuropsychological tests. This makes inter-test comparisons a tricky task. One way of overcoming this limitation, is to derive a reference scale where individual scores in a test battery are statistically related to a single representative scale with equal intervals. The Halstead-Reitan Battery impairment index exemplifies such a scale, although the transformation procedure requires a large representative population (Russell, 1994).

In neuropsychological interpretation, *z*-scores are typically classified according to level of impairment: the standard classification system is presented in Table 5-2.

Table 5-2. Classification of Ability Levels

Classification	*z*-score	% included	lower limit of percentile range
Very superior	≥ 2.0	2.2	98
Superior	+ 1.3 to +2.0	6.7	91
High average	+ 0.6 to +1.3	16.1	75
Average	= 0.6	50.0	25
Low average	- 0.6 to -1.3	16.1	9
Borderline	- 1.3 to -2.0	6.7	2
Impaired	≤ -2.0	2.2	-

(Lezak, 1995, p. 159).

This system of classification provides a useful model for psychometric interpretation in clinical practice. Generally speaking, significant findings are defined in terms of the number of scores falling into the borderline or impaired category, and clinical interpretation involves making neuropsychological sense of clusters of test score deviations.

Considerable variation exists in practice and research in terms of what constitutes neuropsychological impairment. Lezak (1983) recommends that scores equal to or in excess of 2 *SD*s below the mean be regarded as significant, with differences of 1 to 2 *SD*s suggesting a trend; this cut-off was used to define neuropsychological impairment in a recent investigation of HIV infection (McAllister et al., 1992). In contrast, a cut-off score of 1.5 *SD*s below the mean was used to indicate impairment in a study by Hinkin, van Gorp, Weisman, Thommes, and Buckingham (1992), while Krupp et al. (1994) derived indices of impairment based on a rating of the number of test scores lying 1 *SD* below an estimated premorbid level of functioning. In the latter method, neurocognitive functioning was defined as follows: (1) *normal* - zero to three scores 1 *SD* below the mean; (2) *mild to moderate impairment* - four scores 1 *SD* below the mean; and (3) *severe impairment* - 5 or more scores 1 *SD* below the mean.

A variation of this method was used by Skoraszewski, Ball, and Mikulka (1992) who defined *normal* neuropsychological functioning as no more than one test score lying 1 *SD* below the mean, and *impairment* as two or more scores 1 *SD* below the mean. Similar ways of understanding neuropsychological test scores are reported by DeLuca et al. (1995) who derived a neuropsychological impairment index based on *SD*s from the mean of their control group. Specifically, scores for each test measure within 1 *SD* from the control group mean were assigned an IR of 0, test scores that were 1 to 2 *SD*s below the mean were given a rating of 1, whereas scores 2-3 *SD*s below the mean received an IR of 2. Scores greater than 3 *SD*s below the mean earned a rating of 3. Raw scores for each of the 31 test measures were therefore transformed into a summed impairment rating (SIR) for each subject. Recently, Sclafini et al. (1997) employed a slight variation of this rating based on three levels of clinical impairment: scores above the 15th percentile received a rating of 0; scores between the 5th and 15th percentile were given a rating of 1; whereas a score of 2 was given to subjects scoring below the 5th percentile on a particular test.

It appears that such systems of classification are somewhat arbitrarily determined and at present there is no universally accepted system for the analysis of *z*-scores; it therefore remains a clinical rating that is operationalized in different ways by different researchers.

5.2 RATIONALE FOR THE CURRENT STUDY AND STATEMENT OF AIM

Since neuropsychological assessment offers a unique, sensitive and practical method of assessing and evaluating human cognition and brain function/dysfunction, its relevance for the evaluation of cognitive complaints associated with CFS and other similar conditions is clear. However, despite the inherent suitability of neuropsychological assessment for this purpose, there remains a shortage of studies examining deficits in attention, concentration, memory, and general cerebral efficiency in patients with CFS. Such studies are necessary if the nature and processes of subjectively reported cognitive deficits in CFS are to be fully understood. Apart from information which may further an understanding of the conceptual aspects of CFS, neuropsychological evaluations have potential diagnostic and management utility.

Broadly speaking, the overall goal of the present study was to assess objectively some of the neuropsychological problems reported in the CFS literature and to determine the extent to which they may be associated with clinical and other psychometric data. Apart from investigating the general application of neuropsychological tests in this particular patient population, the current study sought to overcome some of the methodological limitations which have characterized previous investigations. This was addressed by: (a) using a representative sample of CFS patients in terms of age, sex, and educational variability; (b) employing suitably matched comparison groups; and (c) using psychometric measures with sufficient sensitivity so as to detect subtle cognitive dysfunction. The specific aim (1), and hypotheses (2) and (3), of this largely investigative research were:

(1) *Aim*:

That CFS-related neuropsychological dysfunction, if present, can be objectively demonstrated using appropriate test procedures. An extension of this aim was to identify neuropsychometric measures/test scores that are best able to discriminate CFS patients from normal and depressed control groups (i.e. to determine whether CFS has a distinct psychometric profile).

(2) *Hypothesis A*:

That given the proposed etiology of persisting viral infection in CFS, a generalized brain disturbance (akin to a subclinical encephalitis) can be predicted as the source of the neuropsychological deficit in CFS. This deficit is most likely to be manifested in impaired cerebral efficiency (encompassing possible deficits in attention, concentration and memory).

(3) *Hypothesis B*:

That neuropsychological deficit, if present, is not attributable to: (i) level of depression or to other psychiatric factors (acceptance of this hypothesis would require that the neuropsychological profiles of depressed and CFS subjects are psychometrically distinct); and (ii) medication side-effects.

CHAPTER 6

METHODOLOGY

6.1 CONSIDERATIONS IN THE DESIGN OF CFS RESEARCH STUDIES

6.1.1 Research Strategy

A number of different research strategies are suitable for the study of chronic fatigue syndrome, although the exact choice will be determined by the research question and aim. Some studies have employed epidemiological designs that focus primarily on aspects of CFS such as prevalence and incidence, time, place and person distributions, and time-space clustering. In contrast, is the more analytical epidemiological approach which attempts to explain the underlying mechanisms behind a particular phenomenon; this latter approach appears to be favoured by psychologists and the medical fraternity. Grufferman (1991) outlines the various types of research designs which are representative of the analytical epidemiological approach:

(1) The *cross-sectional study:*

In which an attempt is made to gather information (such as risk factors) from individuals in order to assess the common factors. However, such approaches often have little to say about etiology and are limited by the "chicken-and-egg dilemma", i.e. it is not always possible to determine what comes first, the disease or the suspected risk factor.

(2) The *follow-up (cohort) study:*

This methodological approach involves following a group of individuals (and their controls) over time in order to assess the disease manifestation of the risk factors of interest. Usually the researcher defines an *exposure* variable (such as CFS) as well as an *outcome* variable (such as opportunistic infection). Drawbacks to this particular approach include the etiological limitations mentioned above as well as the difficulty and expense of following a control group. For this reason many cohort studies compare the exposed group to the general population.

(3) The *case-control study:*

This represents the most popular approach to the study of CFS; essentially the researcher chooses a group of individuals with CFS (cases) and compares them with a comparable group of individuals without CFS (controls). A variety of dependent measures of interest can be used to answer particular research hypotheses. DeLuca et al. (1993) are of the opinion that the use of age-, education-, and intelligence-matched controls is the only acceptable method of evaluating cognitive impairment in CFS, although other demographic variables such as sex, socioeconomic status and occupation could also be important. Despite the interpretative advantages of a case-control design, Grufferman (1991) points out a number of pitfalls which may be encountered using this approach:

(i) firstly, there is the risk that the study may turn into a "fishing expedition", i.e. many different measures may be used in an attempt to predict case group membership, with the danger that some might show significant associations with the disease simply on the basis of random sampling variation (multiple experiment effect). This implies that some care needs to be taken in the design and analysis of case-control studies;

(ii) case definition is important in all case-control studies although the nature of CFS implies that subject homogeneity could be a problem;

(iii) related to (ii) is the possibility that systematic error or sampling bias could arise in the selection process if cases are not representative of all cases in the community from which they are drawn; and

(iv) some care must be taken in the selection of controls (see next section).

6.1.2 Patient Variables

The purpose behind a matched group or case-control design is to control for extraneous variation when the case and control groups are compared; this helps to improve the generalizability of the results. For this reason, the control individuals should be as healthy as possible and be comparable to the case individuals in terms of relevant demographic variables. Matching for age, sex and sociocultural background appears to be the most popular consideration, although neuropsychological studies should also use education as this can be an important predictor of test performance.

The importance of matching according to individual (i.e. pairs of subjects) as opposed to group means is emphasized by Tupper and Rosenblood (1984). These authors point out that failure to do this will "artificially restrict the ordinary random variation of the group means" (p. 150). In turn, this could lead to misleading results. There are other considerations and difficulties associated with matched group designs. For instance, Meehl outlines problems associated with *systematic unmatching* which occurs when matching is made on one extraneous variable with resulting unmatching of the subjects on a new (unidentified) extraneous variable (as cited in Tupper & Rosenblood, 1984). Given the general acceptability of case-control designs in psychological research, a critique of this and other associated merits and demerits of matched group designs is considered to lie beyond the scope of this thesis.

Control subjects are commonly obtained from opportunity sources such as other patients at health care facilities, neighbours or relatives, or from listings of voters or taxpayers (Grufferman, 1991). One popular method is to select controls via random-digit telephone procedures. While this reduces the risk of selection bias, it can be an expensive and time-consuming procedure and probably works best in a homogeneous culture. The use of friends and relative is convenient and inexpensive by comparison, although Grufferman (1991) points out that the use of controls with similar lifestyles and environmental exposure could lead to a situation of overmatching. More specifically, he suggests that a high degree of uniformity will tend to hide any true differences between case individuals and the rest of the population. Other methodological issues of importance in case-control designs include whether one should use

newly diagnosed (incident) cases or patients with existing diagnoses (prevalent cases), as well as the number of controls that are required. Generally speaking, the statistical power of a study increases in the face of a greater number of controls relative to cases; however Grufferman (1991) mentions that choice is largely determined by such factors as case availability and the level of statistical significance that the researcher wishes to set for data analysis.

6.1.3 Assessment of Fatigue

Despite the fact that fatigue is the principal symptom of CFS, definition and measurement thereof appear to be one of the most problematic aspects of the condition. Although there is now some agreement about what constitutes fatigue, the lack of a psychometrically valid measure of fatigue has been recognized as a major hindrance to research (Fisk et al., 1994). This is an anomaly given the availability of instruments that document other subjectively experienced conditions (such as chronic pain). An additional concern is the claim that much of the early research on CFS may have been confounded by the use of imprecise measures of fatigue (Barofsky & Legro, 1991).

The development of the CDC criteria for CFS was an attempt to standardize the meaning of the term *chronic fatigue*. The major criteria were that fatigue should be persistent, relapsing or debilitating, new for the individual, not resolve with bed-rest, and be associated with a 50% reduction in premorbid activity for a period of at least 6 months (Holmes et al., 1988). However, the working case definition was problematic in that it did not specify how fatigue could be measured (one of the difficulties in assessing subjective fatigue is that it means different things to different people). Barofsky and Legro (1991) recognize this issue when they suggest that a fatigue measure should invite the respondent to define his/her meaning of the term fatigue. Such a measure has however not yet appeared in the literature.

A more refined set of criteria is offered by the Oxford criteria which recognize that fatigue may involve both physical and mental dimensions (Sharpe et al., 1991). The authors recommend that in order to be regarded as a symptom, fatigue should:

(a) be complained of;

(b) significantly affect everyday functioning;

(c) be disproportionate to exertion;

(d) represent a clear change from premorbid functioning; and

(e) be persistent or present more than 50% of the time.

(Sharpe et al., 1991, p. 120)

A recommendation is made that fatigue symptoms be rated in terms of severity, frequency, and in relation to minor exertion. In order to make the assessment of fatigue more meaningful, the Oxford criteria also emphasize the importance of assessing the impact of fatigue on everyday activity (e.g. occupational, social, recreational). An attempt to operationalize these criteria in the current study led to the incorporation of questions about subjectively experienced fatigue in the Intake Questionnaire (see Appendix A, p. 294). A similar questionnaire has also been devised by Lloyd et al. (1990) and is an attempt to operationalize their diagnostic criteria.

6.1.4 Selection of Neuropsychological Tests

While the design of neuropsychological test batteries is largely based on purpose and individual preference, certain recommendations can be made with regard to battery structure. In this regard, Kolb and Wishaw (1990) highlight five criteria which they consider to be important. These are: (1) thoroughness; (2) ease and cost; (3) time (of administration); (4) adaptability; and (5) flexibility. A further consideration mentioned by Altay, et al. (1990) is that selected measures should be relatively unaffected by intellectual capacity and educational level. Both Altay et al. (1990) and Grafman, et al. (1991) suggest that test batteries should be comprised of standardized clinical tests that sample relevant areas of neurocognitive functioning in CFS patients (See Table 6-1). According to Grafman et al., this kind of composite battery is sufficiently flexible so as to allow for the inclusion or substitution of additional neuropsychological measures. However, one point of criticism might be that this battery seems somewhat over-inclusive. In addition, "scales of depression, anxiety, and fatigue" hardly qualify as measures of "personality".

Table 6-1. A Representative Neuropsychological Test Battery for CFS

Function tested, suggested tests	Description
Intelligence	
WAIS-R	verbal and nonverbal cognitive abilities
Memory	
Wechsler Memory Scale (revised)	recall, recognition and orientation
California Learning Test	verbal learning/recognition
Continuous Visual Recognition Test	nonverbal recognition
Benton Visual Retention Test	visuoconstructive memory
Implicit/Automatic Memory Task (selected by examiner)	measures non-effortful memory
Attention	
Simple and Choice Reaction Time	response speed and selection
Continuous Performance Test	vigilance and target detection
Posner Spatial Attention Task	focal spatial attention
Language	
Word Fluency	retrieval of items from semantic memory
Personality	
Scales for depression, anxiety and fatigue	emotional distress/psychopathology
Psychiatric Interview	psychiatric diagnosis

(Grafman et al., 1991, p. 50)

The choice of neuropsychological measures used in the current study was based on a number of considerations:

(1) The test battery should be sufficiently broad-based so as to sample a range of both cortical and subcortical neuropsychological functions.

(2) The battery should be reasonably short to avoid assessment-induced fatigue. One of the problems with the battery in Table 6-1 is the length of administration, which could be something in the region of 3 hours. Apart from the issue of cost-effectiveness, using a battery of this magnitude is clearly problematic in terms of administration time for the

fatigued patients. One constraint of the current study was that the test battery should strike a compromise between coverage and administration time.

(3) The battery should include measures capable of detecting the most subtle neurocognitive impairment and be appropriate to the assessment of CFS-related cognitive impairment.

(4) The battery should be comprised of tests that are commercially available so as to allow for cross-validation by other researchers and comparison with other studies.

(5) The individual tests making up the battery should have normative data.

(6) A final consideration lay in the issue of portability, i.e. the battery should permit administration in a hospital clinic or at a patient's place of residence.

Some discussion on these considerations is appropriate. Firstly, given the association of CFS with viral infection in some cases, it seems reasonable to assume that CFS-induced neurocognitive deficits may be associated with a general deficit in brain function akin to what might be expected in cases of subclinical viral encephalitis. Selected tests should therefore be appropriate to the functions most likely to be affected by an infectious process (e.g. mental activity variables such as attention, concentration and mental tracking, and memory). The inclusion of the complete WAIS-R in Figure 6.1 seems somewhat wasteful in this regard. Secondly, although it might have been interesting to construct a test battery that actively fatigues subjects, this was not part of the current design which was largely exploratory in nature, and which aimed to assess existing group differences in neuropsychological functioning.

Thirdly, some of the studies that have examined the neurocognitive domain of CFS have employed measures which may be insensitive to subtle disturbances in brain function. The Wechsler Memory Scale has been used in a number of CFS studies, yet it is limited in that it does not allow one to assess aspects of memory functioning such as rate of acquisition or retrieval efficiency, both of which are likely to be affected by subtle disruption of brain function. This

tendency toward a false negative effect makes it unsuitable for research where one is investigating more subtle forms of neuropsychological impairment. A related problem is the ceiling effect which characterizes some neuropsychological tests; this refers to a clustering of test scores near the upper boundary of the particular scaling measure which is used. In this regard, the clinical experience of the writer suggests that a high score on the *Visual Reproduction* subtest of the Wechsler Memory Scale may be attained by nearly all neurologically intact individuals as well as many patients with mild closed head injury (i.e. the test is not challenging enough to detect subtle impairment). This problem is also shared by the *Digit Span* subtest of the Wechsler Adult Intelligence Scale (WAIS-R), a measure that has been used in a number of recent CFS studies (e.g. Krupp et al., 1994; McDonald et al., 1993; Michiels et al., 1996), despite views that it is a relatively weak measure of neurocognitive functioning (Lezak, 1983). To some extent, the selection of tests in the current study was guided by the emerging field of the neuropsychology of AIDS and HIV infection. These are conditions characterized by subtle brain dysfunction in the early/asymptomatic stages (see footnote on p. 131 for a mention of the parallels between HIV-infection and CFS).

With regard to the fourth point, that of cross-validation, it seems important that given the heterogeneous nature of patient samples used in CFS studies, greater control could be gained, and more valid comparisons made, by using standardized and commercially available tests accessible to most clinicians. Some of the neuropsychological investigations of CFS are weakened by their reliance on less commonly-used or "in-house" laboratory-constructed measures in their designs (e.g. Grafman et al., 1993; Smith et al., 1993). An important and related point not specifically mentioned above, is that selected tests should have acceptable validity and reliability. This is an area which is not enjoyed sufficient attention in neuropsychology (in comparison to tests of personality etc.). Nevertheless, all of the measures which were selected for use in the current study (with the exception of the Visual Design Learning Test), are reasonably well-standardized instruments that are commonly used in research and clinical practice (Spreen & Strauss, 1991). This suggests at least some degree of psychometric acceptability.

The fifth point is problematic. The power of neuropsychological testing is related to the diagnostic precision of the instrument in question, which in turn, is dependent on reliable norms.

There is considerable variation in the extent to which this requirement is met by various neuropsychological measures. As mentioned in the previous chapter, it is not uncommon for published norms to be based on sample sizes as small as 10 individuals (Spreen & Strauss, 1991). This undesirable situation restricts the representativeness of normative data, and is compounded by age, sex and education effects on neuropsychological test performance. Cultural factors may also exert an influence on certain measures (Lezak, 1995). There is no easy way of getting around this problem in neuropsychological research short of developing one's own normative data base; this could be a costly and time-consuming process for any researcher/clinician. It should therefore be apparent that one area of potential experimenter bias lies in the selection of normative reference data. Problems can arise in selecting norms that are outdated, inappropriate in terms of demographic variables, or otherwise unsuitable. A lack of clinical standards in the field does not make this selection any easier. In the writer's personal experience, many South African neuropsychologists rely on test norms that are clearly inappropriate. To minimize the effects of experimenter bias in the current study and to verify the suitability of the proposed normative data, an experienced and highly regarded neuropsychologist was consulted.

The requirements listed above were hopefully met with a reasonable degree of success in the final test selection, and summary descriptions of the tests chosen for inclusion in the current study are presented in the next section. Further information about these measures (including specific administration instructions and scoring procedures) may be found in the relevant manuals as well as in general reference texts such as Lezak (1995), Spreen and Strauss (1991), and Crawford, Parker, and McKinlay (1992).

6.2 NEUROPSYCHOLOGICAL TESTS USED IN THE CURRENT STUDY

6.2.1 Trail Making Test (TMT)

Included as a measure of attention, concentration, and mental tracking, the TMT is a widely used test in clinical and experimental neuropsychology. Performance success also depends on speed and intact visuomotor functioning (especially visuospatial sequencing ability). Sensitivity to even the most subtle forms of brain impairment account for the popularity of this test (Lezak, 1983). It is administered in two parts (A and B). Part A requires the subject to join (with a continuous pencil line) consecutively numbered circles from 1 to 25 as quickly as possible. The more challenging Part B consists of a double or simultaneous tracking task involving number and letter sequences; the subject is required to start on 1, draw a line to A, then from A to 2, to B and so on in as short a time as possible. The dependent measure is the time taken (in seconds) to complete Parts A and B. A negative correlation exists between test score and level of performance (i.e. the lower the score the better the performance). The additional measure of number of errors made on either Parts A or B was recorded in the current study since it was hypothesized that reduced cerebral efficiency in CFS patients might manifest itself in a greater predisposition to making errors. However, this additional measure does not form part of the standard scoring procedure for the TMT.

According to Lezak (1995), reliability coefficients for the TMT vary considerably in terms of the population under study, but for the most part appear to be in the .70 to .90 range (Spreen & Strauss, 1991). Performance varies according to age, sex (in some studies) and especially education. For the latter, Bornstein (1985) reports correlation coefficients of .19 and .33 for Parts A and B respectively (age-related effects partialled out; $N = 365$). Kelland and Lewis (1994) report a test-retest reliability of .74 for Part B (one-week interval).

Various norms are available (Bornstein, 1985; Fromm-Auch & Yeudall, 1983; Spreen & Strauss, 1991; Yeudall, Reddon, Gill, & Stefanyk, 1987). The norms by Bornstein (1985) and Yeudell et al. (1987) were the ones used in the current study.

6.2.2 Symbol Digit Modalities Test (SDMT)

The SDMT (Smith, 1982) is modelled on the *Digit Symbol* subtest of the WAIS but is presented in a reverse format, i.e. the subject is required to locate the symbol in the key and respond with the number. This variation from the *Digit Symbol* format allows the subject to respond with a more familiar number sequence, although this gain is offset by the time taken to locate the symbol in the key (Glosser, Butters & Kaplan, 1977). Essentially, the SDMT is a measure of visual perception, graphomotor speed, concentration and incidental learning (Lezak, 1983; Spreen & Strauss, 1991). It is also administered in two parts, a timed *written* trial which requires the subject to fill in the relevant numbers on the record form, and a timed *oral* administration in which the subject calls out the relevant numbers and these are recorded by the examiner. Ninety seconds are allowed for each trial, the dependent measure being the number of correct responses produced in the time limit.

The dual administration format of the SDMT is useful in that it allows one to partial out the effects of motor slowing on test performance. This is especially relevant for studies in which a depression-induced psychomotor slowing component may be expected. Comparison of the two scores (when a significant discrepancy exists between them) can rule out an information processing problem as the reason for defective performance on the *written* administration. The differential sensitivity of the *oral* version to deficits in speed of information processing has been reported in some recent research on closed head injury (Ponsford & Kinsella, 1992). Only one study to date has used the SDMT in CFS research (Krupp et al., 1994); others have preferred the use of the *Digit Symbol* subtest from the WAIS-R. Krupp and colleagues found the SDMT to be the most sensitive measure in their battery in terms of its ability to discriminate CFS patients from the control groups.

As with the TMT, an additional measure of the number of errors made on the written and oral administrations was recorded in the present study.[42] The norms set out in the manual (by age and sex) are comprehensive (age range 8 to 78), and were the ones used in this study. Significant

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[42] This potentially useful index is not widely used in CFS research; one exception being Michiels et al. (1996).

correlations with education in females (.26 for oral), and with age in males (-.29 for oral; -.19 for written), are reported by Yeudall, Fromm, Reddon, and Stefanyk (1986). Reliability coefficients for the written and oral administrations following a one month retest, were found to be .80 and .76 respectively (Smith, 1982). McCaffrey, Ortega, Orsillo, Nelles, and Haase (1992) report a test-retest reliability of .70 (7 to 10 days interval).

6.2.3 Grooved Pegboard (Lafayette Instrument®)

This measure of motor speed and manual dexterity is a more complex variation of the better-known Purdue Pegboard. It consists of steel pegs and a pegboard with randomly positioned slotted holes in a 5 x 5 array. The pegs are manufactured with a ridge along one side and they are placed in the slots in the pegboard in much the same way as a key might be inserted in a lock (i.e. each peg has to be correctly rotated before it can be inserted in the slot). This difference from the Purdue Pegboard introduces an element of fine motor control which is likely to be sensitive to motor slowing and reduced manipulative dexterity. The dependent measurement is the time taken to insert the pegs into the 25 holes for each of two trials (firstly using the preferred hand, followed by the non-preferred hand). The sensitivity of the Grooved Pegboard to depression and subcortical dysfunction associated with HIV-1 seropositive status, has been demonstrated in recent research (Hinkin et al..1992). In the CFS literature, the Grooved pegboard has been used in only one study (i.e. Riccio et al., 1992). The test manual (Lafayette Instrument®) provides various sets of norms for ages 5 through 60 years. The Grooved Pegboard appears to be a reliable instrument, with a test-retest reliability ranging from .69 to .82 (Kelland & Lewis, 1994; McCaffrey et al., 1992;).

6.2.4 Paced Auditory Serial Addition Task (PASAT)

The PASAT (Gronwall, 1977) is a measure of concentration and information processing efficiency. It is regarded as a sensitive index of overall integrity of brain function, and impaired performance may be seen in the face of relatively minor head injuries and concussion (Brittain,

La Marche, Reeder, Roth, & Boll, 1991). Part of the reason for its success as a neuropsychological instrument is that many head-injured persons, when faced with a cognitive task, tend to sacrifice speed in order to maintain accuracy. This trade-off is not possible on the PASAT; as a consequence, defective performance shows up easily (Ponsford & Kinsella, 1992). The PASAT shows a correlation with the subjective experience of cognitive symptoms (Spreen & Strauss, 1991) and has been used as an indicator of readiness to return to work (Gronwall, 1977). Reliability studies are lacking in the literature, although Egan reports a high internal consistency of the PASAT in a study which found the split-half reliability to be .96 (as cited in Spreen & Strauss, 1991). Correlations with demographic variables such as age, IQ, gender, race, and education have been investigated, but it seems that only age and IQ are significantly related to PASAT performance (Brittain et al., 1991; Roman, Edwall, Buchanon, & Patton, 1991). Of these, age effects are more prominent (Brittain et al., 1991).

The PASAT is presented on a commercially available audio-cassette and consists of four trials of 61 randomly generated single digit numbers. The subject is required to add together pairs of successively presented numbers, i.e. the last digit heard is added to one that immediately precedes it in the sequence. For example, on hearing the sequence of 2-1-8-7-4-9 the subject should respond with 3-9-15-11-13. The same 60 numbers are presented in four successive trials of varying intervals between digit presentations (2.4, 2.0, 1.6 and 1.2 seconds respectively).[43] The PASAT should therefore be seen as a reasonably demanding task involving the reception of an auditory stimulus, a mental calculation and verbal response, and the concurrent inhibition of a response while attending to the next number in the sequence. This makes it sensitive to a wide range of brain impairment. Modified 50-item versions of this test have appeared in the literature in various normative studies (Brittain et al., 1991; Roman et al., 1991). The dependent measure in the Gronwall (1977) version and in the current study was the number of correct responses for each of the four trials. An additional cumulative score was also computed (sum of trials 1 to 4). Credit is only given to responses made in the interval between successive numbers.

43

A sample of the test format may be found in Spreen and Strauss (1991), p. 146.

Due to equipment limitations, a taped version of this test (based on the original version) was locally produced for use in the current study. In keeping with the original, the duration of each spoken digit was approximately 0.5 seconds. Because of the difficult and challenging nature of this test (and on the basis of examiner experience), a slight departure from standard administration instructions was deemed necessary in certain cases. The modification involved greater elaboration of what was required, and consisted of a paper-and-pen demonstration following the practice sample. This was followed by a verbally-guided practice trial and taped practice trial presented at 2.4 second intervals. Consistent with the instructions recommended by Brittain et al. (1991), each subject was told that they would be presented with four separate series of numbers, each separated by an interval, and with subsequent trials being presented at a slightly faster pace. The intervening period between trials was 30 seconds, during which time the tape was left running (a 30 second interval was purposely built in to the design construction of the tape) and the subject was provided with general encouragement.

Choosing a normative reference for this test is problematic owing to the different versions of the test that exist and the inconsistency in the dependent measures reported. For instance, the study by Brittain et al. (1991) converts the number correct score into mean seconds per correct response by using a conversion table. In contrast, Roman et al. (1991) report the number correct for each of the four trials but their norms are stratified into discontinuous age ranges. The norms reported by Spreen and Strauss (1991) are comparable to those of Gronwall (1977) and Roman et al. (1991), and were the ones used in this study.

6.2.5 Controlled Oral Word Association Test (COWAT)

Also known as the FAS Test (Lezak, 1995), this is a measure of verbal productivity under restricting cognitive search conditions. It was included in the present design primarily as an index of overall cerebral efficiency and cognitive flexibility, as well as a measure of verbal functioning. Subjective word-finding difficulty in CFS patients has been reported in earlier research (e.g. Wessely & Powell, 1989). Apart from its sensitivity to brain dysfunction in general (Lezak, 1983), performance on the COWAT is especially affected by frontal lesions (Spreen &

Strauss, 1991). In addition, performance is relatively unaffected by depressive symptomatology (Lezak, 1983), making this an ideal measure for inclusion in a CFS battery. To this extent, it has been used in a number of CFS studies (Cope et al., 1995; Grafman et al., 1993; Krupp et al., 1994; Riccio et al., 1992). One-year test-retest reliability has been reported by Snow to be .70 (as cited in Spreen & Strauss, 1991). Correlations with age (-.19) and education (.32) are reported by Yeudell et al. (1986), necessitating the use of demographically appropriate normative data.

The COWAT is administered in three trials in which the subject is instructed to orally generate as many words as possible in one minute beginning with the letter "*F*". This is followed by second and third trials using the letters "*A*" and "*S*" respectively. Proper names, plurals and close variations on words already presented are not permissible.[44] For scoring purposes, the examiner writes down all of the words produced by the subject and credits the number of permissible responses for the three letters. The total and average number of words generated across the three trials have appeared in some normative studies (Yeudell et al., 1986).

The selection of norms for this test is also problematic; Yeudell and colleagues present comprehensive norms for a healthy sample of 255 subjects aged between 15 and 40 years. However, there is a shortage of published normative data for both older and younger subjects. Spreen and Strauss (1991) give data for subjects aged 50-75 years, although only the summed total across three trials is presented. Where necessary, normative data from the closest matched group was used in this study.

6.2.6 Memory Tests

Given the large number of memory tests available to neuropsychologists, the choice of which one to use is largely governed by clinical judgement and the research question under investigation. In this study, the choice was determined by two main requirements:

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[44] For example, the word "eating" would be an unacceptable variation of "eat".

(1) The test should yield information relevant to the research question. Previous research suggests that memory deficits are associated with CFS (Millon et al., 1989), but measures such as the Wechsler Memory Scale are somewhat insensitive and not very informative about the actual processes underlying memory disturbance. For this reason, the study required a measure that would yield information on such aspects as rate and quality of acquisition/learning, susceptibility to interference, stimulus overload, retrieval efficiency, predisposition to errors, and recognition memory.

(2) The test should provide similar types of information for both verbal and non-verbal memory. This would allow for direct material-specific comparisons. A dissociation between verbal and non-verbal memory is often indicative of a material-specific memory deficit associated with lateralized brain dysfunction (Walsh, 1991). Although this was not expected to be a prominent finding in the current study, there are some indications of specific verbal or auditory deficits in CFS (De Luca et al., 1993; Riccio et al., 1992) .

These requirements (taken together) are not met by any existing memory scale or battery, and so a composite memory battery made up of two similar tests (one verbal, one non-verbal), was assembled. Although not specifically mentioned in the points above, accessibility of test material was a further consideration in the current design.

(i) *Auditory-Verbal Learning Test (AVLT)*

The AVLT was devised by Swiss psychologist Andre Rey (as cited in Spreen & Strauss, 1991) and has become a widely-used test of verbal memory and new learning (Wiens, McMinn, & Crossen, 1988). It consists of a list of 15 words (List A) which is read out to the subject at a rate of one word per second and the subject is then asked to recall as many of them as possible in any order that they like (see Table 6-2 below). This is repeated for an additional four trials; in each case the examiner records the order of the words recalled as well as any deviations from the original list. Deviations could consist of intrusions (words not on the list) or modifications of the List A words. The time allowed for recall is 60 seconds for the first trial followed by 90 seconds

for trials 2 to 5. Following the final learning trial (Trial 5), the examiner introduces a distractor list of 15 additional words (List B or Trial 6) which is read out and which the subject has to recall. This is followed in turn by a request for the subject to recall as many words as possible from List A (delayed recall trial or Trial 7).

A recognition trial containing the 15 words from List A as well as some distractor words from List B and words not previously presented is commonly administered. Various formats exist for the recognition trial; some clinicians use a story paragraph in which the List A words are embedded and which is presented to the subject with the instruction to read it through and verbally identify or circle the recognized words from List A. Others use a list of 50 words that contains all of the words from Lists A and B as well as words that are semantically associated with or phonemically similar to the words on Lists A or B. The story recognition format was used in the present study (see Table 6-2). Finally, the subject is asked to recall the words from List A following a 20-minute delay period (long-term recall trial or Trial 8).

Table 6-2. Word Lists and Story Recognition Format from the Auditory-Verbal Learning Test

List A	List B	Story Recognition
Drum	Desk	
Curtain	Ranger	The teacher swallowed his *coffee* quickly and
Bell	Bird	hurried down the road toward the *river*. He
Coffee	Shoe	crossed the bridge and tipped his *hat* to the
School	Stove	*farmer* cleaning his *turkey* pen. Every minute
Parent	Mountain	or so, he wiped his forehead and *nose* with his
Moon	Glasses	handkerchief. He arrived at the *school house*
Garden	Towel	just as the last *bell* rang. His *moon* face was
Hat	Cloud	the *colour* of a *garden* beet. Through the
Farmer	Boat	classroom *curtain* he saw a *parent* pace the floor
Nose	Lamb	while the children played soldier with a broomstick
Turkey	Gun	gun and a *drum*.
Colour	Pencil	
House	Church	
River	Fish	

(Lezak, 1976, pp.353-355).

The AVLT yields a number of parameters useful in the assessment of memory functioning. In clinical practice, the totals for the eight individual trials are usually reported. Examination of scores for the first five trials gives some indication of the quality of the learning curve (i.e. verbal learning ability). Proactive interference can be assessed by comparing recall on the first administration of List A with recall on the distractor trial (List B). Likewise, retroactive interference can be assessed by comparing the number of words recalled on Trials 5 and 7. Research has shown the recognition trial to be relatively insensitive to differences in age and IQ in normal populations; this makes it an ideal measure to use when assessing pathology (Wiens et al., 1988).

Additional learning indices have been reported in some studies. Query and Megran (1983) report an index based on the highest number of words recalled on any of the first five trials, minus the recall score on Trial 1. Ivnik et al. (1990) report a slight variation on this formula; they derived a *learning over trials* index which is equal to the total words for Trials 1 to 5, minus five times the number of words recalled on Trial 1. Wiens et al. (1988) report a percentage recall score (defined as the number of words recalled on the post-distractor list [Trial 7] divided by the total words recalled on Trial 5). The AVLT also lends itself well to qualitative analysis. According to Peaker and Stewart (1989), the occurrence of intrusions (i.e. words not included in Lists A and B) reflects a possible breakdown in self-monitoring function. Lezak (1983) notes that a loss of three or more words from Trial 5 to Trial 7 is an abnormal amount of shrinkage and could reflect a retention or retrieval problem. These and other variations reported in the literature (e.g. Forrester & Geffen, 1991; Ivnik et al., 1990; Mungas, 1983; Peaker & Stewart, 1989; Wiens et al., 1988) include:

(a) cumulative learning index (the total number of words recalled in 5 trials);

(b) the number of errors (extra-list intrusions or phonetic errors);

(c) memory for source (defined as the number of cross-list intrusions, i.e. List A words found in List B and vice versa);

(d) serial positions of recalled words (five categories);

(e) forgetting (comparing Trials 7 and 8);

(f) information overload (a comparison of recall on Trial 1 with the *Digits Forwards*

score on the WAIS);

(g) retrieval efficiency (ratio between delayed recall trial [Trial 8] and Recognition Trial);

(h) repetitions (words repeated in first 5 trials);

(i) learning over trials (cumulative learning index minus five times Trial 1); and

(j) percentage retention computations (for data recalled at Trial 6 [STPR] and for a delayed recall trial [LTPR}; both expressed as a percentage of Trial 5 recall, the last learning trial).

The clinical utility of these indices has not yet been convincingly demonstrated; they should therefore be regarded as additional measures in need of cross-validation with clinical samples and other larger normative groups. On the other hand, they are potentially useful indices for research purposes and some were included in the current design. Ivnik et al. (1990) found that their learning over trials index was a better estimate of an individuals's actual improvement over trials than other learning indices; they suggest that this is because it uses information from all five learning trials. A breakdown of the AVLT measures selected for use in the current study is outlined below:

(1) individual scores for Trials 1 to 8,

(2) total words correctly recalled (Trials 1 to 5),

(3) number of errors (Trials 1 to 5 total, also Trials 6,7 and 8),

(4) repetitions (Trials 1 to 5)

(5) learning index (highest score of Trials 1 to 5 minus Trial 1),

(6) learning over trials (cumulative score of Trials 1 to 5 minus five times Trial 1),

(7) short term percent retention index (defined as the percentage of words retained from Trial 5 to 7),

(8) long term (i.e. 20 minute) recall (Trial 9); this was also expressed as a percentage of Trial 5 recall (i.e. long term percent retention - LTPR),

(9) errors on Trial 9.

(10) recognition trial (number of items correctly identified)

In a study by Snow, the one year test-retest reliability of the AVLT (score unspecified) was found to be modest at .55 (as cited in Spreen & Strauss, 1991), although Franzen (1989) has emphasized the need for further reliability studies. The available normative studies suggest that AVLT scores decrease with advancing age, that a positive correlation exists with IQ, and that females outperform males on all but the recognition trials (Spreen & Strauss, 1991). However, appropriate and reliable normative data based on large healthy samples is lacking in the literature. Query and Megran (1983) provide norms for a large group of individuals ($N = 677$), but they tested only males and report data for only four indices. Four sets of normative data were used in the current study. For the most part the norms of Geffen, Moar, O'Hanlon, Clark, and Geffen (1990) were used, although data from Query and Megran (1983) was used to score the recognition trial. The adolescent protocols (cases 10, 13, 30, 33, 50, 53) were scored using Forrester and Geffen (1991), and Spreen and Strauss (1991) for the recognition trial.

(ii) *Visual Design Learning Test* (VDLT)

Developed by Andre Rey as a non-verbal analogue of the AVLT (as cited in Spreen & Strauss, 1991), the VDLT was deployed in this study as a measure of non-verbal memory. Despite its potential to provide similar kinds of information as the AVLT, the VDLT remains surprisingly under-utilized in clinical practice. This may in part be due to the lack of normative studies, although Spreen and Strauss comment on a low test-retest reliability ($r = 0.45$) and significant practice effects after a one month interval. Nevertheless, it was selected in preference to the more popular *Visual Reproduction* subtest of the Wechsler Memory Scale in order to avoid the ceiling effect described earlier and to allow for a more direct comparison with indices of the AVLT. Like the AVLT, it is presented over five trials, and consists of 15 simple geometric designs (on cards) presented at a time at a rate of two seconds per card (see Spreen & Strauss, p. 169). The subject is required to recall as many of the designs as possible following five repeated exposures of the 15 cards. At the end of the fifth trial the subject is given a blank record form and is shown the recognition sheet (Spreen & Strauss, p. 170) and asked to identify (by number) the original stimulus items. Scoring is relatively straightforward, the individual items for Trials 1 to 5 are scored for accuracy using the scoring guide provided by Spreen and Strauss. Omissions and errors may also be recorded. In a deviation from standard administration instructions, a delayed

recall trial (20 minutes) was implemented so as to allow for comparison with the AVLT. Dependent measures used in this study therefore consisted of the following:

(1) individual scores for Trials 1 to 5, and Total (1 to 5);
(2) number of errors (Trials 1 to 5 and the Recognition Trial);
(3) learning index (as for AVLT);
(4) learning over trials (as for AVLT);
(5) recognition trial (number items correctly identified);
(6) long term (20 minute) recall; and
(7) long term percent retention (as for AVLT).

The norms provided by Spreen and Strauss (1991) were used to evaluate subject performance although there is no normative data for the error scores, learning index and long-term recall scores listed above. Like the AVLT, performance on the Recognition Trial appears to be insensitive to age effects (ibid).

6.3 PSYCHOLOGICAL QUESTIONNAIRES

Some of the considerations mentioned in previous section are applicable to the selection of self-report inventories. Tests like the Sixteen Personality Factor (16 PF) and Minnesota Multiphasic Personality Inventory (MMPI) exemplify the more traditional approach to the objective assessment of personality and psychopathology. However, widespread acceptance of psychiatric diagnostic classification systems such as the DSM-III-R appears to have precipitated the development of new and cost-effective measures which bear a more direct link to these classification systems. The Millon Clinical Multiaxial Inventory (MCMI), its revisions (MCMI-II and MCMI-III), and the revised edition of the Symptom Checklist 90 (SCL-90-R) are examples of such measures.

6.3.1 Symptom Checklist 90-R(evised) (SCL-90-R)

The SCL-90-R (Derogatis, 1983) was chosen as the principal instrument of psychopathology assessment in this study for two reasons. Firstly, it is economical in clinical practice, taking only 12-15 minutes to complete (compared to 25-30 minutes in the MCMI and longer for the MMPI). Secondly, it covers a wide range of clinical symptoms and is therefore an ideal screening device for the assessment of psychopathology. The merits of both these points are reflected in the increasingly popular use of the SCL-90-R in research and practice (Thase, 1991). It is particularly favoured by neuropsychologists (e.g. Lezak, 1989) who are faced with the administration of an often lengthy neuropsychological battery to their patients and who require a short but reliable method of assessing psychological symptoms. A further reason for its inclusion, lies in the claimed sensitivity of the SCL-90-R to depressive syndromes (Thase, 1991). Finally, Grafman et al. (1991) recommend the use of a mood state inventory that does not rely too heavily on the physical (vegetative) aspects of depression (e.g. loss of sexual interest). This latter point is of considerable importance in CFS research since it has been demonstrated that endorsement of physical complaints by patients with CFS will artificially elevate their depression scores on instruments that emphasize this aspect of depression (ibid). The SCL-90-R meets this requirement and has been used in a number of recent investigations into CFS (Egle et al. 1996; Valadini et al., 1989; Vercoulen, 1994) and fibromyalgia (Kirmayer et al., 1988). In comparing the diagnostic efficiency of the SCL-90-R and MCMI in evaluating major depression, Wetzler, Kahn, Strauman, and Dubro, (1989) found the *Dysthymia* scale of the MCMI and *Depression* scale of the SCL-90-R to be equally efficient in the diagnosis of depression. Finally, the construction of the SCL-90-R has allowed for differential recording of the affective, cognitive and somatic symptoms associated with depression (these factors are respectively labelled *Depression*, *Obsessive-Compulsive* and *Somatization*).

The SCL-90-R comprises a 90-item self-report inventory "designed to reflect psychological symptom status in a broad spectrum of individuals, ranging from normal respondents, through medical patients of various types, to individuals with psychiatric disorders" (Derogatis, 1983, p. 5). Respondents are invited to respond to each item by rating the degree to which the symptom has distressed or bothered them in the past seven days. A five-point scale of distress is used to assess the severity of each complaint from 0 = *not at all*, to 4 = *extremely*

distressed. Scores from the individual items are assembled into nine symptom dimensions (see Table 6-3 below) which were developed "through a combination of clinical/rational and empirical/analytical procedures" (Derogatis, 1983, p. 5). The last dimension is made up of seven items that were found to load on several of the dimensions but are not specific to any of them; they were retained on the basis of clinical importance and for their contribution to the global scores (ibid). Three global scores are computed: the *Global Severity Index (GSI)* - a measure of the level or magnitude of the individual's distress, the *Positive Symptom Total (PST)* - a pure intensity measure corrected for the number of symptoms, and the *Positive Symptom distress Index (PSDI)* - the symptomatic "breadth" of the individual's distress. The symptom dimensions and global ratings are converted to *T*-scores using sex and patient status determined conversion tables in the manual. It is suitable for adolescents as young as 13 years. A positive diagnosis or "case" is defined as a *GSI* score greater than or equal to a *T*-score of 63, or any two primary dimension scores greater than equal to a *T*-score of 63.

Table 6-3. Symptom dimensions of the Symptom Checklist 90 - R(evised)

(1) Somatization
(2) Obsessive-Compulsive
(3) Interpersonal Sensitivity
(4) Depression
(5) Anxiety
(6) Hostility
(7) Phobic Anxiety
(8) Paranoid Ideation
(9) Psychoticism
(10) Additional

(Derogatis, 1983)

A number of independent validational studies of the SCL-90-R are reported in the test manual, while Thase (1991) regards it as a reasonably robust instrument. Test-retest coefficients on the symptom dimensions range from .78 to .90 (Derogatis, 1983). The general acceptability of this instrument is reflected in its increasing appearance in the literature.

It is evident that most CFS studies have employed some rating of depressive symptomatology in their designs. The most commonly used instrument is the Beck Depression Inventory (Beck, Ward, Mendelson, & Erbaugh, 1961) and it appears to be a standard in the field of depression research. However, the Zung Self-Rating Depression Scale (Zung, 1965)[45] and others, such as the Center for Epidemiologic Studies Depression Scale (CES-D), have also been used in CFS studies (Krupp et al., 1994). The CES-D enjoys a high correlation (.73 to .89) with the SCL-90-R *Depression* scale according to Weissman, Sholomskas, Pottenger, Prusoff, and Locke (1977). The diagnostic comparability of the depression/dysthymia subscales of the MCMI, MMPI, and SCL-90-R scales were compared by Wetzler, Kahn, Strauman, and Dubro (1989). All three subscales offered similar levels of diagnostic efficiency in the diagnosis of major depression.

6.3.2 Cognitive Failures Questionnaire (CFQ)

Originally devised by Broadbent, Cooper, FitzGerald, and Parkes (1982) to assess minor everyday mental slips or errors, the CFQ is a measure of self-reported failures in perception, memory and motor function. Such failures are not uncommon in CFS patients (see case study at the start of Chapter 4). A similar example of cognitive failure in a non-CFS individual is presented by Broadbent and colleagues when they relate the story of a flight engineer who repeatedly miscalculated the safe load of fuel to retain in a (simulated) aircraft during an emergency landing, and who finally concluded that his instruments must be in error! These kinds of difficulties are apparently commonplace in normal individuals and are generally ascribed to (unspecified) stress (ibid). The directionality of this relationship is not well established although Broadbent and colleagues are of the impression that stress results from cognitive failure rather than stress being a precipitant of cognitive failure.

Broadbent et al. (1982) drew on their personal experiences of everyday cognitive failures

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[45] Reservations about the validity and utility of the Zung SDS have been expressed by Hamilton (1992) who concludes that although it has seen extensive use, "a number of reports have indicated that it is not as satisfactory as was once thought" (p. 10). For instance, correlations with the more widely used Hamilton Rating Scale of depression (HAM-D), range from 0.4 to 0.79 (ibid).

to devise a questionnaire of twenty-five items rated on a four-point Likert-type scale (see Appendix B, p. 301). While being a potentially useful instrument in psychological research, there is again a noticeable lack of normative data and independent validation of the psychometric properties of the CFQ. Broadbent et al. report correlations ranging between .57 and .62 in terms of the CFQ's relationship with similar instruments; it also shows relative independence from test intelligence (correlation of -.15 with the Progressive Matrices; $N = 51$) and educational level (-.16 correlation with the Mill Hill; $N = 128$). Test-retest reliability at a 15-month follow-up, is reported to be in the region of .80 ($N = 32$), although reliability coefficients from a series of studies reviewed by the authors range from .54 to .82. In terms of correlations with psychiatric instruments such as the Middlesex Hospital Questionnaire (a symptom inventory sensitive to neuroticism), the CFQ shows significant correlations with anxiety and depression. However, the association between the CFQ and commonly used neuropsychological instruments is unknown. This gap in the literature is surprising, given the view of Hickox and Sunderland (1992) that "items on the CFQ.... appear to have considerable relevance to the problems of memory, concentration, and poor self-monitoring ability frequently experienced by brain-injured patients" (pp.106-107). Part of the rationale for the inclusion of the CFQ in the current study was therefore not only to get an index of subjective neurocognitive dysfunction in CFS patients, but also to explore its relationship with commonly used neuropsychological measures. This has not been done in either of the two published studies that have employed the CFQ in CFS research (Smith, 1992; Smith et al., 1993).

6.3.3 CFS Symptom Checklist

The range of symptoms associated with CFS is presented in Chapter 1. It is evident that most studies have attempted to document these subjectively reported symptoms. This was also considered to be an important inclusion in the current study since it gives some idea of the scope and severity of CFS symptoms, and allows for comparison with related research. Berne (1992) provides a useful checklist in this regard. It consists of 41 commonly experienced symptoms and 20 additional symptoms (experienced by less than 10% of patients). Subjects are required to rate the severity of each symptom on a scale from 0-10. An adaptation of this scale was used in the current study: modifications consisted of dropping the additional symptoms and rating scale, and

merging a couple of the related symptoms into one item. The rationale for this simplification was that an examination and measurement of CFS-related symptoms was not the focus of the research, and also that it was not being used for diagnostic purposes. The end result was a checklist of 39 items (see Appendix C, p. 302). Subjects were asked to read through the various symptoms and simply endorse (with a tick) any symptoms they had experienced in the past six months. An overall summary score (*Total Score* [maximum = 39]) was computed for use in the statistical analysis.

6.3.4 Intake Questionnaire

The difficulties inherent in the objective evaluation of subjective fatigue have already been addressed. It is important in CFS research to have at least some indication of the nature and severity of subjectively experienced fatigue and related symptoms. Following the definitions and recommendations of Sharpe et al. (1991), an intake questionnaire was assembled with the aim of operationalizing some of the diagnostic criteria specified in the Oxford criteria (although again, the aim was descriptive rather than diagnostic in purpose). The result was a questionnaire (see Appendix A, p. 294) that sampled dimensions of physical and mental fatigue, myalgia, and mood and sleep disturbances. Where possible, the behavioural dimension was categorized to permit limited group comparisons.

Also included in this questionnaire was a section detailing relevant biographical information. The questionnaire was introduced to each subject with some explanation of its relevance and purpose (this was especially important for the control group subjects). In order to reduce the chance of contamination from rapidly fluctuating symptoms, subjects were instructed to fill in the questionnaire with reference to events experienced in the past month.

6.4 STUDY SUBJECTS

The case control nature of the design involved the comparison of three groups of subjects; a group of CFS patients ($n = 20$) and two groups of age-, sex-, and education-matched controls. A match for occupation was also attempted and achieved in 11 of the 20 matched "triads" of subjects (60%).[46] The control groups were comprised of 20 depressed and 20 healthy subjects. The inclusion of a depressed control group in the research design was considered to be important given the reported symptom overlap between depression and CFS (Calabrese et al., 1992; Wessely, 1993). Study exclusion criteria consisted of the following:

(1) presence of a recurrent or chronic medical condition that could potentially interfere with normal neuropsychological functioning (e.g. hypertension, diabetes, asthma, etc.);

(2) a history of neurological illness such as head injury, epilepsy, cerebrovascular disorder (including migraine), or acute brain infection (e.g. meningitis or encephalitis); minor concussion without loss of consciousness was not considered as reason for exclusion unless there was evidence of medical attention or hospital treatment or residual neurological/cognitive sequelae;

(3) a history of learning difficulty or Attention Deficit Hyperactivity Disorder (ADHD);

(4) age in excess of 69 years (owing to the lack of reliable neuropsychological test norms for this age group at the time of implementation of this study);

(5) a history of mental illness (this was defined as diagnosis of, or treatment for, severe psychopathology exemplified by conditions such as psychosis, bipolar affective disorder and severe personality disorder);

(6) a history of chronic fatigue syndrome in control group subjects;

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[46] Each triad consisted of an age-, sex- and education-matched individual from each of the three groups (CFS, depressed, and healthy)

(7) a history of substance abuse; however, no attempt was made to control for current prescription drug use; and

(8) a first language other than English.

6.4.1 CFS Subjects ($n = 20$)

Prior to recruitment of the CFS subjects, contact was made with four medical doctors who had interest and expertise in the diagnosis and treatment of patients with chronic fatigue syndrome; two were family practitioners, one was a virologist, and the other a psychiatrist. This was done to gauge local expert opinion on the clinical syndrome of CFS as well as ascertain prevalence, availability of subjects, and current treatment approaches in South Africa. In each case the doctors were asked to refer suitable patients for assessment. In addition, contact was made with two regional M.E. support groups (one in Pietermaritzburg and the other in Durban). A third source of subjects came from an announcement of the research study in a local newspaper.

As the first step of the patient recruitment, each prospective candidate who had received a medical diagnosis of CFS and who met the Oxford criteria, was sent an information letter outlining the nature of the study and an intake questionnaire which was designed to assess the nature and extent of the principal symptoms of CFS. Following approximately 45 telephonic enquiries about the research study, 40 intake questionnaires were sent out and 36 were returned. Of these, nine were excluded from further involvement in the study for the following reasons: a lack of neuropsychological normative data for one elderly subject aged 72 years; neurological conditions in six subjects (one with a history of head injury, one with epilepsy, two with a history of chronic migraines, one with a history of meningitis, and one with a history of encephalitis); one subject became medically ill prior to testing, and the final exclusion was due to a self-report of substantial recovery in one patient. A telephonic follow-up was attempted on the four outstanding prospective participants; three were reluctant to participate for various reasons, while one had relocated and could not be contacted.

A total of 27 CFS patients were tested although seven of these were excluded for the following reasons: one patient was tested as part of a pilot study in which an incomplete test battery was administered; one participant was of a different race group and matched controls could not be found; one patient was experiencing severe marital problems which impacted on her test performance (see later comment), while the diagnosis of CFS was dubious in four cases (exclusion followed consultation with the doctors concerned).

The CFS group was comprised of 20 subjects with an age range of 13 to 64 years (mean = 37.35 years). The ratio of males to females was 1:4 (4 males versus 16 females). While it could be argued that this is a fairly small sample of subjects, the demographics compare favourably with some of the larger overseas studies, indicating that a representative sample of CFS patients was used in the current study. For example, Komaroff and Buchwald (1991) report a median age of 37 years in their study of 250 CFS patients, while Manu et al. (1993) report a female bias in incidence of 70% ($N = 405$). The sample also closely resembles that of Fisk et al. (1994) who found a mean age of 37.8 years and male female ratio of 1:4 (29 males versus 116 females). The inclusion of two adolescents in the current study also reflects some of the growing awareness of the prevalence of CFS in this particular age group (Bell et al. 1994; Vereker, 1992).

6.4.2 Depressed Subjects ($n = 20$)

The depressed subjects were recruited from various mental health professionals (three psychiatrists and four clinical psychologists). Approximately 60% (12 subjects) were referred directly from the in-patient and out-patients facilities at the local psychiatric hospital, while one was referred from the psychiatric ward of a large general hospital. The remaining seven patients were referred by clinical psychologists. Apart from fulfilling the matching criteria of age, sex and education, all subjects in the depressed group had to meet the following inclusion criteria based on the *Diagnostic and Statistical Manual of Mental Disorders* (3rd edition, revised)(APA, 1987) - see Table 6-4. According to the DSM-III-R, the symptoms had to be present for a minimum of two weeks and have been experienced every day or nearly every day during that time. Two potential patients were excluded from the study for failure to meet the criteria in Table 6-4 (the

anti-depressant medication had exerted the desired therapeutic effect in the delay between referral and initiation of testing), while an additional three patients were excluded on the basis of a neurological history in one subject, and a previous diagnosis of chronic fatigue syndrome in two subjects.

Table 6-4. Inclusion Criteria for Depressed Control Group

Either of the following two major symptoms and at least four of the associated features:

Major symptoms:

(1) depressed mood; *or*

(2) markedly diminished interest or pleasure in all or almost all activities.

Associated features:

(3) significant weight loss or weight gain (e.g. ± 5% of body weight in a month), decrease/increase in appetite;

(4) insomnia or hypersomnia;

(5) psychomotor agitation or retardation;

(6) fatigue or loss of energy;

(7) feelings of worthlessness or inappropriate guilt;

(8) impaired concentration; indecisiveness;

(9) recurrent thoughts of death; suicidal ideation or recent attempt.

(APA, 1987, pp. 222-223).

No attempt was made in the current study to grade the severity of depression and so it is possible that a heterogeneous group was selected. The clinical impression of the writer was that approximately half of the subjects were clearly experiencing a major depressive episode; the remainder appeared to be more dysthymic or mildly depressed. In the neuropsychologically-oriented CFS studies which have employed depressed controls, it appears that group composition has been largely heterogeneous in terms of variables such as history and severity (Cope et al., 1995; DeLuca et al. 1995; Marshall et al. 1997; Schmaling et al., 1994). Thase (1991) acknowledges the heterogeneity of depressive syndromes but is of the opinion that a clinical diagnosis that fulfills the DSM-III-R criteria is perfectly adequate. He notes however that diagnostic precision can be increased through the use of psychometric rating scales and/or standardized semi-structured or structured interview techniques. The depressed control group

in the De Luca et al. study was comprised of DSM-III-R diagnosed dysthymia and major depression in an unspecified composition. Cope et al. (1995) used an outpatient depressed control group who received an ICD-10 diagnosis of either mild or moderate depression, while Schmaling et al. (1994) and Sandman et al. (1993) used patients with major depression as defined (respectively) by the Inventory to Diagnose Depression (IDD) and DSM-III-R criteria (APA, 1987). It seems that there are no clear guidelines in the CFS literature on how a depressed control group should be comprised in terms of the variables mentioned above, although Schwartz et al. (1994) suggest that patients with dysthymia or milder depression may be more appropriate controls than patients with severe depression who are usually hospitalized (see comment by Banich, 1997 below).

The majority of depressed patients (60%) were on medication at the time of assessment; this contrasts with eight medicated CFS patients (40%) who were on antidepressants, and none of the healthy controls. Research has indicated that while elderly persons may be susceptible to mild medication-related cognitive dysfunction (Marcopulous & Graves, 1990), this is less of a problem for younger patients (Killian, Holzman, Davis, & Gibbons, 1984). Although an ideal study would control for the effects of medication by excluding those taking it, one encounters ethical difficulties on the part of doctors who have a legal responsibility to patients under their care and who are justifiably uneasy about withholding medications from potentially suicidal individuals. In the only study that reports having controlled for this variable (Sandman et al., 1993), patients were admitted to a psychiatric inpatient service where medication could be stopped under supervision. This was not possible in the current study. Additionally, Banich (1997) suggests that the use of hospitalised patients in neuropsychological research introduces a new set of uncontrolled variables that could impact negatively on neurocognitive functioning.

6.4.3 Healthy Controls ($n = 20$)

The healthy group was an opportunity sample derived from various sources. One convenient source came from friends and acquaintances of the case individuals. One advantage of this approach to sampling is that it allows for a high degree of matching on variables such as age, education and occupation. Other suitable controls came from friends and associates of

colleagues. Approximately 25 individuals were approached for participation in the study; a lack of interest was expressed in three cases while another two were tested but later excluded when more exact matches to the CFS and depressed groups became available. Subject characteristics are presented in Table 6-5. Additional demographic details are presented in Table 6-6.

Table 6-5. Demographic Profiles of Subjects Used in the Current Study ($N = 60$)

Variable	CFS ($n = 20$)	Depressed ($n = 20$)	Healthy ($n = 20$)
Mean age in years	37.35 (13.30)	37.55 (13.46)	37.35 (13.25)
Age range	13 - 64	13 - 62	13 - 63
Male female ratio	1:4	1:4	1:4
Mean education (years)	13.10 (2.73)	13.15 (2.89)	13.40 (2.82)

Note: age and education figures presented as mean and *SD* (in parentheses).

Table 6-6. Demographic Breakdown (Age by Education) of Study Subjects ($N = 60$)

Age	Count	% of total
10-19	7	11.67
20-29	8	13.33
30-39	17	28.33
40-49	18	30.00
50-59	7	11.67
60-69	3	5.00
Education (years)	**Count**	**% of total**
< 8	3	5.00
9-12	26	43.33
13-15	17	28.33
>15	14	23.33

(See Appendix D. p. 304 for a complete listing of subject demographic details)

As a result of the careful matching procedure, there were no group differences with respect to age (F [2,57] = .002, p = .998), or education (F [2,57] = .065, p = .937) using one-way ANOVA (Norusis/SPSS Inc., 1988).

6.5 PROCEDURE

Following subject selection, individual appointments were arranged for each subject. The assessments were conducted at a suitable venue at the University of Natal (Pietermaritzburg) for the majority of subjects. Alternative but suitable assessment venues at the local hospitals were used for four depressed subjects while one CFS subject was assessed at home on her request (she insisted that she was too fatigued to travel). One of the school-going depressed subjects was assessed during school hours in a suitable venue at school.

Attempts were made to minimize the possible effects of fatigue on test performance by arranging for the tests to be administered in the morning (one exception was a CFS subject who made a specific request that he be tested in the afternoon owing to debilitating morning fatigue). This follows the advice of Lezak (1983) who maintains that assessments should be scheduled early in the day so as to optimize test performance in easily fatigued (brain-injured) patients. Given that fatigue is the cardinal feature of CFS, this was considered to be an appropriate strategy. However, it is acknowledged that a variety of other environmental, psychological and physiological conditions can affect human test performance and these were not controlled for in the present study. For example, research has shown that circadian rhythms have an effect on behavioural measures; psychomotor speed measures tend to peak in the afternoon while measures of short-term memory show a morning superiority (Campbell, 1992). Such phenomena are reflected in electrophysiological changes; Wesensten, Badia, & Harsh (1990) showed that the *P300* (an index of information processing) is sensitive to time of day effects. Other factors that could potentially affect human test performance are almost too numerous to mention, but include: ambient temperature and humidity, core body temperature, blood-sugar level, hormonal changes associated with the menstrual cycle, drugs (including exposure to nicotine and caffeine), quantity of recent sleep, colds and influenza, noise, atmospheric ionization levels, and non-specific fatigue (Campbell, 1992; Lezak, 1983; Reilly, Atkinson, & Waterhouse, 1997; Smith & Jones, 1992).

The initial data collection consisted of a brief interview (15-20 minutes) which included:

(1) an explanation of the purpose of the research study and the signing of a consent form (additional parental consent was obtained for subjects aged under 18 years);

(2) completion of the intake questionnaire for the control group subjects, and experimenter enquiry into any aspect thereof that required elaboration. This was followed by completion of the CFS Symptom Checklist and Cognitive Failures Questionnaire (CFQ);

(3) enquiry into relevant areas not included in the intake questionnaire (e.g. history of learning disability etc.) and elaboration of any questions raised spontaneously or in response to completion of the CFS Symptom Checklist and CFQ.

The neuropsychological assessment followed the interview and the various tests were administered in a fixed order format. It could be argued that a random administration order might have been preferable for this particular patient group in that it would minimize the effects of cumulative fatigue on specific test instruments. However, this was not implemented for two reasons. Firstly, it was thought that some of the tests were perhaps more anxiety provoking and/or challenging than others (e.g. PASAT) and that it might be unwise for the testing session to begin with such tests. Secondly, two of the tests (AVLT and VDLT) incorporate a delay procedure, the timing of which could become complicated in a random order format. Subsequent research by Schmaling et al. (1994) suggested that the placement of a challenging measure at the beginning of their assessment battery may have caused their subjects to feel overwhelmed, thereby impacting negatively on test performance; they encourage others to administer some easier tasks early on so as to facilitate adaptation to the testing procedures. According to Cope et al. (1995) the advantage of a fixed order presentation sequence is that it controls for performance fatigue, although Lezak (1995), in a review of research in this area, concludes that the order of test presentation does not have an appreciable effect on test performance. The order of test presentation and approximate administration times were as follows:

1. Grooved Pegboard (4 minutes)
2. Trail Making Test (5 minutes)
3. Symbol Digit Modalities Test (5 minutes)
4. Auditory-Verbal Learning Test (10 minutes)
5. Visual Design Learning Test (10 minutes)
6. Paced Auditory Serial Addition Task (15 minutes)

7. AVLT - delayed recall (1 minute)
8. COWAT (4 minutes)
9. VDLT - delayed recall (2 minutes)
10. SCL-90-R (10-15 minutes)

The administration of the neuropsychological tests was conducted in accordance with the instructions specified in the various test manuals and sources. In addition, they were administered by the experimenter in a fashion consistent with standard clinical practice which offers general encouragement to subjects and attempts to ensure optimal performance throughout. Enquiries as to the subjective physical status of each subject was made prior to commencement of the testing. This was done to ensure that none of the subjects were excessively fatigued, drowsy or experiencing distracting drug side-effects. All subjects were offered a few minutes break at any time if they felt overwhelmed, although this offer was not taken up by any of the subjects.

Test administration mistakes are a potential source of error in research of this nature. Fortunately, the clinical experience of the examiner ensured that these were kept to a minimum. Nevertheless, subtle variations in the pacing to the words on the AVLT and exposure times of the VDLT cards were unavoidable. In addition, a timing error on the Grooved Pegboard necessitated a retrial for one subject.

The time taken for the administration of these tests was approximately 60-70 minutes. Slight inter-subject variation in the timing of the delayed incidental recall trials of the AVLT and VDLT was unavoidable, although none of the subjects were tested in under 20 minutes or over 30 minutes (the AVLT was probably closer to 20-25 minutes and the VDLT closer to 25-30 minutes). Such a discrepancy is not regarded as a significant source of error given the relative stability of memory traces over the duration of an hour (Lezak, 1983).

From an observational perspective, the test-taking behaviour was appropriate in all cases and participants appeared to give their best performance throughout. Many of the subjects reported the PASAT to be the most difficult test although only one depressed subject appeared to give up on the 4th trial. One additional healthy control subject experienced difficulty comprehending the requirements of the PASAT and the practice trial had to be repeated a few

times. Some subjects appeared to overwhelmed by the first trial of the VDLT and complained of stimulus overload. For many subjects, the COWAT was perceived to be a challenging task, with one or two cases claiming that they "hit a blank" and were not able to generate as many words as they thought they were entitled to.

The assessment procedure was interrupted for a few minutes in only one case when the subject (CFS group) became tearful and was clearly distracted. Despite offers to abort the testing she elected to continue although this case was later discarded from the sample.[47] All subjects were paid for their participation in the study, except that the CFS patients were offered feedback on their results as an alternative option; this was taken up by seven subjects. Two of the healthy subjects and one depressed patient refused payment for their participation.

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[47] This subject appeared to be clinically depressed during the assessment. Subsequent consultation with the referring medical practitioner and with the subject herself, revealed current severe marital problems; these had not been fully disclosed to the examiner or referring doctor prior to the assessment. Since optimal test performance could not be guaranteed, a decision was taken to discard her data.

6.6 TREATMENT OF RAW DATA

Following data collection (which spanned a seven month period from May through November 1994), the individual tests were scored according to the directions specified by the various test manuals and sources. The role of subjective judgement in the scoring of any of the tests used in this research was considered to be minimal, thereby obviating the need to establish inter-rater reliability. In the measures where a clerical scoring mistake could easily be made (such as in the SCL-90-R or SDMT) the scoring was independently verified by a psychology graduate as a check on scoring accuracy. The psychometric summary score sheets for the 60 subjects may be obtained from the writer (a sample is included in Appendix E, p. 306).

Each test score was then entered into an electronic data file (see disk file - CFSDATA) which was again independently checked for transposition errors. A final check for the accuracy of data entry was made by examining the value distributions of the raw scores. Two additional (and smaller) data files were assembled for specific statistical procedures. One was based on a rearranged order of subjects to allow for non-parametric analysis of the data (see disk file - TRIPLETS); the second was comprised of *z*-scores derived from the neuropsychological test data (see disk file - ZSCORE). In constructing this latter data file the various test scores from each subject were evaluated with reference to published normative data. Appendix F (p. 307) contains the variable lists for the CFSDATA and ZSCORE data files.

CHAPTER 7

RESULTS

7.1 OVERVIEW AND RATIONALE OF STATISTICAL ANALYSIS

The results were analyzed using SPSS/PC+™ (Norusis/SPSS Inc.,1988a, 1988b) and an alpha of .05 accepted as the significance level. As a first step, the data distributions were examined using the SPSS/PC+™ EXAMINE procedure (SPSS Inc., 1989). This command allows for the investigation of normality (K-S Lilliefors test) and homogeneity of variance (Levene statistic). Of the 54 individual neuropsychological test scores, 38 (70%) were identified as having non-normal distributions (these were examined separately for each group), whereas two scores (3.7%) were found to display heterogeneous variance (Trial 6 and Recognition score, both of the AVLT). The Levene statistic was not computed by SPSS/PC+™ for a further eight scores (i.e. in cases where the median was not positive; spread-and-level plots were therefore not generated). Representative examples where this situation arose, include the number of errors on certain trials of the AVLT and VDLT. Heterogeneous variance and non-normal distributions also characterized the SCL-90-R raw scores (the Levene statistic reached level of significance in five of the nine subscale scores; it was not computed for the *Phobic Anxiety* scale).

According to Lezak and Gray (1991), non-normal distributions and heterogeneous variances are not uncommon findings in neuropsychological research. Norusis/SPSS Inc. (1988a) maintain that most data deviates slightly from the normal distribution, but that this becomes problematic only where there are large deviations. Specifically, it is suggested that "analysis of variance procedures are reasonably robust to departures from normality" (p. 22). Unfortunately, there does not seem to be any reliable method for demonstrating this *robustness.*

Since it could be argued that abnormal distributions and heterogeneous variances constitute a violation of the assumptions of parametric ANOVA, two procedures were implemented. Firstly, square root transformations were performed to stabilize the variances in

the 16 cases mentioned above; unfortunately these transformations were successful only for the SCL-90-R scores (spread-and-level plots could not be generated for the neuropsychological test scores). Secondly, in cases where ANOVA assumptions were still not met (i.e. in the transformed scores), nonparametric procedures were employed to evaluate group differences. For this, the raw score database was reassembled into a format that allowed for an equivalent to the randomized block design (see below) in which each case was compared with two matched controls. A Friedman two-way ANOVA (group by case) was then employed to investigate group differences.

For the parametric inter-group comparisons (analysis of variance or ANOVA) the test data were cast into a randomized two-way block design[48] that permitted comparison of triads of subjects (i.e. CFS, depressed and healthy). This was done to capitalize on the fairly precise matching of subjects in the present study, and follows the recommendation of Grufferman (1991) who suggests that matching done in the design phase should be maintained in the analysis phase. Specifically, the subjects were ranked on the basis of age and education (i.e. the matching determinants) to form a block (triad). In other words, the data analysis (parametric and nonparametric) treated the matched case-control individuals as units (triads) rather than as an unmatched series of cases and controls that could be analyzed using a more conventional ANOVA.[49]

Post hoc comparisons were made using *t*-tests (two-tailed), and a Bonferonni correction (.017) was applied to control for multiple experiment effect (Everitt, 1996). The importance of the latter point for neuropsychology is emphasized by Egan (1992), who states that chance variation may account for particular set of results when using large test batteries if one does not control for

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48

This format is otherwise known as *matched random assignment* (Neale & Liebert, 1980). It is used to counterbalance the possible effects that preexisting subject characteristics might have on the dependent measure (Kazdin, 1992); in this case, age and education are likely to influence neuropsychological test performance. It is essentially an endeavour to minimize error variance by employing a matching technique. Using this procedure, the matched triads of subjects are randomly assigned to the conditions of the experiment. Kazdin (1992) states that the advantage of this procedure is that "it does not leave to chance the equivalence of groups on the characteristic(s) of interest" (p. 89).

49

For the remainder of this chapter, the term "ANOVA" is used to describe the two-way ANOVA described above.

making multiple statistical comparisons between groups.

In short, both parametric and nonparametric statistics were computed, and while it might be argued that this practice is unnecessary or even undesirable, precedents are apparent in the scientific literature (e.g. Ray et al., 1993; Snorrason et al., 1996). Scanning the published neuropsychological literature, one gains the impression that parametric statistical techniques are the preferred method for evaluating study results, yet there seems to be no simple explanation as to why nonparametric procedures would be inappropriate. Generally speaking, parametric statistics are regarded as being more powerful than nonparametric procedures because of the smaller sample size that is required to achieve the same level of significance, and also because they have a reputation for being fairly robust in the face of assumption violations (e.g. variance and homogeneity). However not all statisticians are in agreement on this point; Greene and d'Oliveira (1978) suggest that there is no compelling reason against using nonparametric tests. Indeed, Lehman (1991) suggests that recent research is beginning to question the parametric robustness assumption. A more important consideration is offered by Lezak and Gray (1984); they argue that the acceptance of the robustness of parametric tests, also means accepting that the Type 1 error may be overestimated, hence making the test less powerful. The net result is an increased scope for missing a potentially significant finding. This observation has particular importance for neuropsychological research where "small sample sizes, high variances, uneven distributions, and missing observations work together to reduce the likelihood that comparisons between groups will be appropriately analyzed with parametric statistics" (Lezak & Gray, 1984, p. 17). Additionally, Clark and Ryan (1993) point out that in neuropsychological studies where one might expect some samples of subjects to demonstrate impairment, statistical power may be lost in parametric analyses due to increased sample variance.

In addition to the univariate statistical comparisons outlined above, the neuropsychological test scores were converted into standard scores (*z*-scores) so as to facilitate a more clinical evaluation of the test data and scope of neuropsychological impairment (see pp. 166-167). For the most part, statistical procedures consisted of cross-tabulations (Norusis/SPSS Inc., 1988a), and sources of association were isolated using the Lancaster and Irwin method of table partitioning (Everitt, 1977). All statistical procedures may be obtained from the writer.

7.2 RELIABILITY

Inter-item reliability for the 54 neuropsychological measures (see Table 7-9) was computed (Cronbach alphas); results indicated a somewhat modest overall alpha of .64. Reliability coefficients for the questionnaires were more satisfactory (.97 for the Cognitive Failures Questionnaire and .98 for the SCL-90-R). The SCL-90-R reliability index is similar to the figure obtained by Vercoulen et al. (1994) in their investigation of 298 CFS patients (.91), while the CFQ coefficient is better than the .89 alpha reported by Broadbent et al. (1982). There is a notable dearth of studies reporting the internal consistency of neuropsychological tests when applied to clinical samples, and so no comparisons are reported here.

7.3 PSYCHOLOGICAL QUESTIONNAIRES

7.3.1 Intake Questionnaire

As mentioned in the previous chapter, the intake questionnaire was employed to gather relevant background data and to provide a crude subjective measure of fatigue. Some of the relevant data collected by the intake questionnaires is summarized in Table 7-1. Unless otherwise stated, the data refers to the percentage of individuals endorsing a particular symptom dimension. Descriptive statistics of the questionnaire are provided on disk, and so Table 7-1 should be read in conjunction with reference to the actual questionnaire and the appropriate disk file(s). No statistical comparisons were computed for the questionnaire data, its main purpose being to explore the spectrum of subjective complaints and the impact of these complaints on everyday functioning.

Table 7-1. Intake Questionnaire Data (Sample Percentages) by Group (CFS, Depressed, Healthy)

Symptom		CFS ($n = 20$)	Depressed ($n = 20$)	Healthy ($n = 20$)
Severity of physical fatigue:	none	0	15	60
	mild	0	45	35
	moderate	65	35	5
	severe	35	5	0
Severity of mental fatigue rating:	none	0	5	50
	mild	20	25	50
	moderate	55	60	0
	severe	25	10	0
Frequency of physical fatigue	none	0	10	55
	seldom	0	15	15
	sometimes	30	55	30
	continuous	70	20	0
Frequency of mental fatigue	none	0	0	50
	seldom	10	10	15
	sometimes	35	65	35
	continuous	55	25	0
% individuals reporting physical fatigue worsened by exertion		95	25	5
% individuals reporting mental fatigue worsened by exertion		90	35	5
Fatigue related disability:				
occupational:	not applicable	0	40	100
	diminished	60	55	0
	complete loss	40	5	0
social:	not applicable	0	40	100
	diminished	15	60	0
	complete loss	85	0	0

Table 7-1 (continued). Intake Questionnaire Data (Sample Percentages) by Group (CFS, Depressed, Healthy)

Symptom			CFS (n = 20)	Depressed (n = 20)	Healthy (n = 20)
Fatigue related disability.					
	recreational:	not applicable	0	50	95
		diminished	65	50	5
		complete loss	35	0	0
Mood disturbance:					
	depression	none	10	0	75
		mild	30	0	25
		moderate	35	65	0
		severe	25	35	0
	loss of pleasure	none	15	5	75
		mild	20	10	25
		moderate	40	65	0
		severe	25	20	0
	anxiety	none	5	0	70
		mild	15	5	25
		moderate	40	40	5
		severe	40	55	0
	mood	none	0	0	75
	changeability	mild	25	15	10
		moderate	35	50	15
		severe	40	35	0
	irritability	none	5	0	55
		mild	25	20	35
		moderate	30	45	10
		severe	40	35	0
Myalgia		no	5	90	95
		yes	95	10	5
	%individuals reporting myalgia worsened by exertion		95	5	0

Table 7-1 (continued). Intake Questionnaire Data (Sample Percentages) by Group (CFS, Depressed, Healthy)

Symptom		CFS (n = 20)	Depressed (n = 20)	Healthy (n = 20)
Severity of muscle pain:	none	0	90	95
	mild	10	10	0
	moderate	50	0	0
	severe	40	0	5
% subjects reporting sleep disturbance:		100	90	25
Type of disturbance:	hypersomnia	20	10	0
	insomnia	40	60	20
	both	40	20	5

7.3.2 *CFS Symptom Checklist*

The CFS Symptom Checklist was administered to all three groups; the results appear in Table 7-2. ANOVA revealed a group difference (F [2,39] = 80.57, p = .000) for the Checklist *Total Score*, while a series of post hoc t-test comparisons indicated clear differentiation of all three groups (CFS > depressed, t [38] = 5.66, p = .000; CFS > healthy, t [36] = 10.48, p = .000; and depressed > healthy, t [36] = 5.98, p = .000).

The CFS Symptom Checklist *Total Score* was also examined in terms of its association with other variables. There were no significant correlations with any of the neuropsychological variables, although it was found to be significantly related to the CFQ *Total Score* (r = .75, p < .001), and all of the SCL-90-R subscales.

Table 7-2. Frequency of Reported Symptoms from the Symptom Checklist by Group (CFS, Depressed, Healthy)

	Frequency (%)		
Symptom	CFS (n = 20)	Depressed (n = 20)	Healthy (n = 20)
1. Physical fatigue	100	85	65
2. Mental fatigue	100	95	35
(a) attentional deficits	95	80	30
(b) calculation difficulties	85	40	0
(c) memory disturbance	95	70	0
(d) spatial disorientation	70	0	0
(e) frequently saying wrong word	75	30	0
3. Psychological problems			
(a) depression	80	100	35
(b) anxiety	75	95	30
(c) personality changes	60	35	0
(d) mood swings	85	85	25
4. Nervous system problems			
(a) sleep disturbance	95	85	30
(b) headaches	95	45	25
(c) changes in visual acuity	75	0	0
(d) numb/tingling sensations	70	35	0
(e) clouding of consciousness	80	25	0
(f) frequent unusual nightmares	60	40	0
(g) difficulty moving tongue	65	0	0
(h) hearing disturbance	75	0	0
(i) severe muscular weakness	90	0	0
(j) blackouts	100	0	0
(k) intolerance of bright lights	90	0	0
(l) intolerance of alcohol	50	0	0
(m) alteration of taste/smell	55	25	0
(n) non-restorative sleep	95	55	0
(o) decreased libido	65	25	0
(p) muscle twitches	70	0	0

Table 7-2 (continued). Frequency of Reported Symptoms from the Symptom Checklist by Group (CFS, Depressed, Healthy)

Symptom	Frequency (%) CFS (n = 20)	Depressed (n = 20)	Healthy (n = 20)
(q) recurrent flu-like illness	80	25	0
(r) painful lymph nodes	60	0	0
(s) nasal or other allergies	60	30	0
(t) weight change	75	55	0
(u) muscle and joint aches	95	0	0
(v) abdominal symptoms	65	50	0
(w) low grade fever	85	30	0
(x) night sweats	70	35	0
(aa) heart palpitations	70	25	0
(bb) severe premenstrual syndrome	45	40	0
(cc) outbreak of fever blisters	100	0	0
(dd) uncomfortable or recurrent urination	50	30	0
Questionnaire Total Score (mean; *SD* in parentheses)	28.35** (8.39)	14.60[a] (5.89)	4.83 (4.03)

**significantly different from control groups: p < .001; [a] significantly different from healthy controls: p < .001.

7.3.3 Cognitive Failures Questionnaire (CFQ)

Data (means and *SD*s) of the Cognitive Failures Questionnaire (CFQ) are presented in Table 7-3.

Table 7-3. Cognitive Failures Questionnaire Scores (Mean and *SD*) by Group (CFS, Depressed, Healthy)

CFS (n = 20)	Depressed (n = 20)	Healthy (n = 20)	ANOVA (df = 2,19) F	p-value
67.90 (17.08)**	48.95 (15.20)[a]	33.05 (10.35)	23.23	.000

**significantly different from depressed group: p < .001; [a] significantly different from healthy controls: p < .001.

Group differences were also evident for this measure ($p = .000$), while a similar series of t-test comparisons revealed a difference between the CFS group and both control groups (t [38] = 3.71, p = .001; and t [38] = 7.80, p = .000 for the depressed and healthy comparisons respectively); and between the depressed and healthy subjects (t [38] = 3.87, p = .000).

In order to determine which CFQ items were most discriminating in terms of group separation, a Discriminant Functions Analysis (DFA) was performed. It may be noted that while DFA is a commonly employed technique in psychological studies, validity is dependent on a subject-to-variable ratio of at least five subjects for every predictor variable of interest (Rourke, Costa, Cicchetti, Adams, and Plasterk, 1991). Adams (1979) suggests that in general, 10 subjects per variable are required to produce replicable results, the absolute minimum to produce coherent results is three subjects per variable, although he remarks that in this instance, replication would be unlikely. Since these recommended ratios could not be entertained in the current results analysis (60 subjects versus 25 items; ratio = 2.4), the DFA was preceded by a factor analysis to allow for a reduction of CFQ items entered into the DFA. A preliminary correlation matrix of the CFQ items suggested a high inter-item correlation, as well as significant correlations ($p < .01$) of the CFQ Total Score with the 25 individual items (correlations ranged from .55 on Item 11 - *Do you leave important letters unanswered for days?*, to .87 on Item 13 - *Do you fail to see what you want in a supermarket, although it's there?)*.

Four factors (accounting for 71% of the total variance) were extracted in the factor analysis (varimax rotation) before eigenvalues dropped below one (this is the recommended default criterion in SPSS/PC+™); these were:

Factor 1 - Items 2 (.71), 6 (.63), 14 (.61), 17 (.64), 21 (.73), 22 (.73), 23 (.71);
Factor 2 - Items 4 (.83), 5 (.71), 12 (.74);
Factor 3 - Items 11 (.74), 24 (.62), 25 (.67);
Factor 4 - Items 7 (.85), 20 (.74);

It is interesting to note that the CFQ items extracted in the first factor appear to be associated with memory, and specifically with what might be termed *behavioural memory* (Item

22 perhaps less so). Factor 2 items (4,5, and 12), appear to be related to *visuospatial processes* (particularly directionality and perception of the body in space). Functions loading on Factor 3, are less easy to identify by comparison, although the two items comprising Factor 4 (Items 7 and 20) appear to load on memory *forgetfulness*, and specifically to encoding and retrieval difficulties.

In the DFA, three of these factors (Factors 1,3 and 4), successfully discriminated the CFS, depressed, and healthy groups (respective Wilks' lambda were: .51 for Factor 3, $p < .000$; .41 for Factor 3, $p <.000$; and .37 for Factor 4, $p < .000$). F-limits were reached after extraction of this last factor. Canonical discriminant function coefficients were: .60, .62, and -.01 for the respective factors F1, F3 and F4. The results of the DFA revealed that these factors were successful in classifying 70% of the CFS and depressed subjects, and 85% of the healthy individuals. The overall correct classification was 75% (see details in Table 7-4). Individual CFQ items contributing to this classification are shown in Table 7-5, and also depicted in Figure 7-1. Given that the lower the Wilks' lambda, the better the discriminating power, it follows that items 7 and 20 provide the best predictors of the model. As mentioned, these items appear to have, at their source, a reliance on efficient memory encoding and retrieval.

Table 7-4. CFQ Discriminant Function Analysis Classification Matrix

Group	% correct classification	Predicted Classification (number of individuals)		
		CFS	Depressed	Healthy
CFS	70	14	5	1
Depressed	70	3	14	3
Healthy	85	0	3	17

Table 7-5. CFQ Items Showing the Highest DFA Group (CFS, Depressed, Healthy) Classification Ability

2 - *Do you find you forget why you went from one part of the house to the other?*

6 - *Do you find you forget whether you've turned off a light or fire or locked the house?*

7 - *Do you fail to listen to people's names when you are meeting them?*

11 - *Do you leave important letters unanswered for days?*

14 - *Do you find yourself suddenly wondering whether you've used a word correctly?*

17 - *Do you forget where you put something like a newspaper or a book?*

20 - *Do you find you forget people's names?*

21 - *Do you start doing one thing at home and get distracted into doing something else?*

22 - *Do you find you can't remember something although it's "on the tip of the tongue"?*

23 - *Do you find you forget what you came to the shops to buy?*

24 - *Do you drop things?*

25 - *Do you find you can't think of anything to say?*

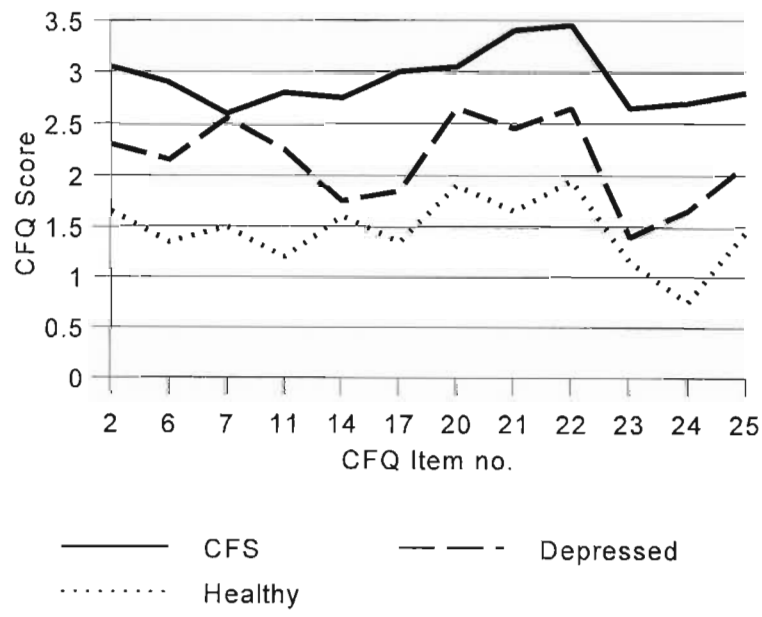

Figure 7-1. Graphical Representation of CFQ Items Showing Highest DFA Group Classification Ability.

7.3.4 Symptom Checklist 90-R(evised) (SCL-90-R)

SCL-90-R data of CFS patients, depressed individuals, and healthy subjects are depicted in Table 7-6. Overall analyses revealed significant group differences on all subscales ($p < .05$ in all group effects), while post hoc *t*-test comparisons comparing CFS with healthy controls, and CFS versus depressed subjects, indicated a number of scales which differentiated the three groups.

From these results, it may be noted that considerable overlap exists between the CFS and depressed groups on the SCL-90-R scores; only two of the nine symptom dimensions differentiated CFS from depressed patients (*Somatization* and *Obsessive-Compulsive*). In contrast, the healthy subjects appear to form a distinct group that shares few SCL-90-R attributes with the CFS and depressed patients.

Table 7-6. SCL-90-R Scores (Mean and *SD*) by Group (CFS, Depressed, Healthy)

	CFS	Depressed	Healthy	ANOVA (df=2,19)	
Subscale	(n = 20)	(n = 20)	(n = 20)	F	p-value
SOM	22.70 (10.40)	10.45 (8.87)**	3.20 (4.55)** [b]	44.10	.000
OBS	22.50 (7.40)	16.90 (6.70)*	8.25 (5.11)** [b]	23.16	.000
SEN	11.25 (8.26)	14.70 (9.49)	4.40 (3.99)*[b]	13.81	.000
DEP	21.90 (9.41)	25.95 (10.88)	7.30 (7.73)** [b]	26.26	.000
ANX	16.25 (9.77)	13.45 (9.30)	3.40 (3.12)**[b]	19.45	.000
HOS	7.75 (5.24)	7.65 (6.70)	2.75 (4.52)*[b]	9.08	.009
PHOB	5.50 (5.83)	4.85 (5.97)	0.15 (0.37)**[b]	14.07	.000
PAR	6.10 (4.59)	7.25 (5.75)	2.55 (3.12)*[a]	6.38	.004
PSY	8.95 (5.96)	9.50 (7.33)	2.05 (3.93)**[b]	19.60	.000

SOM = Somatization, OBS = Obsessive-Compulsive, SEN = Interpersonal Sensitivity, DEP = Depression, ANX = Anxiety, HOS = Hostility, PHOB = Phobic Anxiety, PAR = Paranoid Ideation, PSY = Psychoticism

*significantly different from CFS: p <.05; ** significantly different from CFS: p < .001;

[a] significantly different from depressed: p <.01; [b] significantly different from depressed: p <.001.

Note: high scores indicate greater pathology

In order to document the clinical significance of the SCL-90-R results, the raw data was transformed into age and sex-corrected *T*-scores using the conversion tables provided in the test manual (Derogatis, 1983); the profiles are depicted in Figure 7-2. This procedure also involves the computation of three additional scales; the *Global Severity Index (GSI)*, *Positive Symptom Total (PST)*, and *Positive Symptom Distress Index (PSDI)*. These additional scales represent global indices of distress, the function being to "communicate in a single score the level or depth of the individual's psychopathology" (ibid, p. 11). A clinically significant profile or *casesness* is defined by Derogatis, as a *GSI* score greater than or equal to *T*-score 63, or any two primary dimension scores being greater than or equal to *T*-score 63.

Using this classification system, 90% of the individuals of both the CFS and depressed groups (i.e. 18 individuals in each group) fell into the positive case category, compared with 20% (four individuals) of the healthy group; see Figure 7-3. A Chi-squared analysis revealed this categorization to be significant (χ^2 [2] = 29.42, $p < .001$).

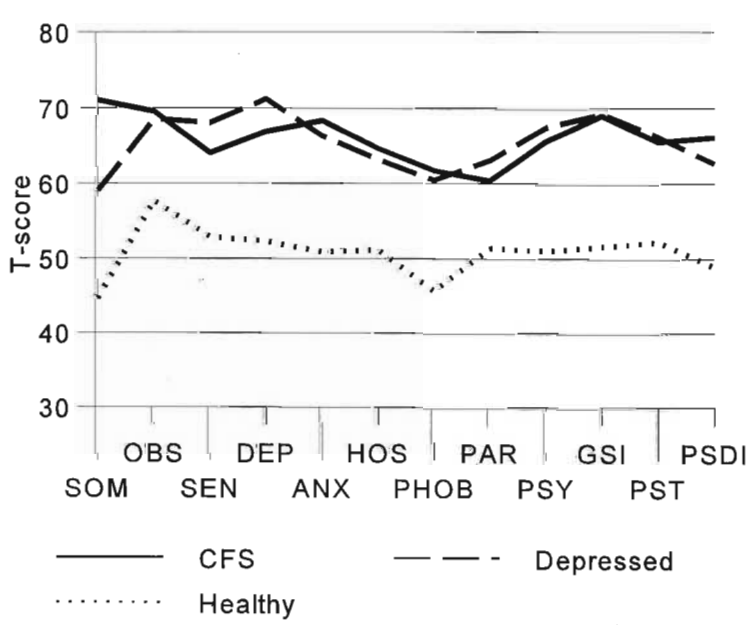

Figure 7-2. SCL-90-R *T*-Score Profiles for CFS and Control Groups.

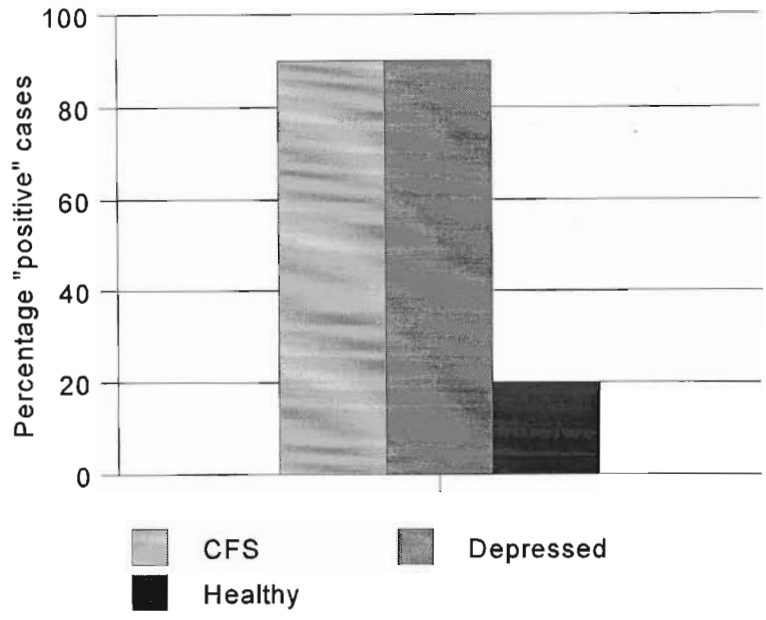

Figure 7-3. Histogram Showing Relative Percentages of Positive Cases on the SCL-90-R.

The SCL-90-R *T*-scores were also entered into a DFA to ascertain which scales best predicted group membership. Four of the twelve SCL-90-R scales were included in the analysis before *F*-levels were reached; these were (with respective Wilks' lambda): *Somatization* (.43), *Depression* (.31), *Phobic Anxiety* (.28), and *Hostility* (.27). Significance levels of $p = .000$ were evident for all of these variables. Canonical discriminant function coefficients were: .78 (*Somatization*), .20 (*Depression*), -.18 (*Hostility*), and .31 (*Phobic Anxiety*). These variables allowed for an overall classification rate of 81.67% - see Table 7-7 for details.

Table 7-7. SCL-90-R Discriminant Function Analysis Classification Matrix

Group	% correct classification	Predicted Classification (number of individuals)		
		CFS	Depressed	Healthy
CFS	75	15	4	1
Depressed	80	3	16	1
Healthy	90	1	1	18

Finally, in order to ascertain the prevalence of clinically significant depression across the CFS and control groups, the SCL-90-R *Depression* subscale *T*-scores were compared. Derogatis (1983) recommends a *T*-score cut-off point of 70 in the identification of major depression, and this allowed for a 67% correct classification rate of depressed individuals ($n = 48$) in a subsequent study by Wetzler, Kahn, Strauman, and Dubro (1989). Table 7-8 summarizes the *Depression* subscale *T*-scores across the three groups in the current study using $T = 70$ as a cut-off for identifying clinically significant depression. A Chi-squared analysis of the distribution of classified individuals was significant at the 95% confidence limit for the partitioned CFS/depressed versus healthy comparison (χ_2^2 [1] = 8.10, $p < .05$), but not for the CFS versus depressed comparison (χ_1^2 [1] = 0.49, $p > .05$).

Table 7-8. Mean SCL-90-R *Depression* Subscale *T*-Scores (SD in Parentheses), and Frequency of *T*-Scores > 70 for the CFS, Depressed and Healthy Groups

	CFS ($n = 20$)	Depressed ($n = 20$)	Healthy ($n = 20$)
Mean (SD)	66.90 (11.09)	71.20 (6.96)	52.30 (11.28)
Range	34-81	58-81	29-76
Number of individuals with $T > 70$.	7 (35%)	9 (45%)	1 (5%)

7.4 NEUROPSYCHOLOGICAL FINDINGS

The results of the various neuropsychological test scores/indices are summarized in Table 7-9. As a first step, MANOVA was performed using group (CFS, depressed, healthy) as a within-subject variable and representative neuropsychological test scores as the dependent variables. Results failed to demonstrate a group difference for a selected set of summary measures.[50] However, since the assumption of a multivariate normal distribution could not be guaranteed, separate univariate ANOVA's were also performed.[51] It should be noted that non-parametric *p*-values (Friedman two-way ANOVA), are presented for the measures indicated by the letters "FRD" in parentheses (*F*-value reported as Chi-square statistic); these are instances in which the square-root transformations either failed to equalize the variances (Levene statistic) or where the success of transformation could not be ascertained due to a failure to generate spread-and-level plots.

Table 7-9. Neuropsychological Test Scores (Mean and *SD*) by Group (CFS, Depressed, and Healthy)

Measure	CFS ($n = 20$)	Depressed ($n = 20$)	Healthy ($n = 20$)	ANOVA ($df = 2,19$) F	p-value
Grooved Pegboard					
(preferred hand)	64.20 (6.17)	62.75 (10.76)	60.50 (9.71)	1.21	.309
(non-preferred hand)	71.95 (9.91)	71.65 (12.46)	66.95 (10.15)	1.29	.286
TMT (Part A)	32.00 (8.86)	34.05 (13.15)	28.40 (9.93)	1.73	.191
Part A errors	0.20 (0.41)	0.10 (0.31)	0.00 (0.00)	0.90	.638 (FRD)
TMT (Part B)	70.20 (25.38)	73.75 (22.77)	65.70 (27.10)	1.30	.285
Part B errors	0.35 (0.93)	0.30 (0.47)	0.10 (0.45)	1.08	.584 (FRD)

50

Selected variables consisted of all test indices from the Grooved Pegboard, Trail Making Test, Symbol Digit Modalities Test; the Total scores (i.e. sum of individual trials) of the COWAT and PASAT; the conventional AVLT and VDLT indices, and the 30 minute recall trials of the AVLT and VDLT.

51

Norusis/SPSS Inc. (1988b) notes that even in instances where individual variables are normally distributed (which was not the case in this research) this does not necessarily imply a multivariate normal distribution when the variables are considered together. The robustness argument again applies here.

Table 7-9 (continued). Neuropsychological Test Scores (Mean and *SD*) by Group (CFS, Depressed, and Healthy)

Measure	CFS (n = 20)	Depressed (n = 20)	Healthy (n = 20)	ANOVA (df = 2,19) F	p-value
SDMT (Written)	51.65 (12.06)	51.70 (10.66)	53.85 (8.03)	0.62	.545
Written errors	0.80 (1.24)	0.30 (0.47)	0.65 (1.23)	1.43	.490 (FRD)
SDMT (Oral)	56.25 (12.00)	57.45 (12.08)	60.55 (9.71)	1.52	.233
Oral errors	0.45 (0.60)	0.40 (0.88)	0.50 (0.95)	0.78	.679 (FRD)
PASAT (Trial 1)	32.70 (10.55)	35.65 (11.14)	38.00 (13.02)	1.44	.249
(Trial 2)	26.00 (7.51)	28.85 (10.41)	30.35 (10.24)	1.38	.264
(Trial 3)	21.00 (5.79)	24.60 (8.57)	24.00 (7.72)	1.41	.256
(Trial 4)	14.65 (4.84)	16.65 (9.32)	17.20 (5.59)	0.95	.396
Total Trials 1-4	94.35 (24.11)	105.75 (32.50)	109.55 (32.57)	1.82	.176
COWAT (F)	12.50 (4.08)	13.70 (3.25)	15.20 (3.46)	2.60	.088
(A)	10.05 (3.76)	10.85 (3.72)	11.60 (3.08)	1.17	.322
(S)	12.40 (4.04)	14.30 (4.39)	16.10 (4.67) [a]	3.30	.048*
Total Trials (F+A+S)	34.85 (10.58)	38.85 (9.02)	42.40 (9.28)	2.89	.068
Average Trials (F+A+S)	11.50 (3.61)	12.95 (3.03)	14.10 (3.09)	3.00	.061
AVLT (Trial 1)	6.55 (1.54)	6.75 (1.68)	7.65 (1.60)	3.48	.041*
(Trial 2)	10.15 (2.06)	9.70 (2.18)	9.60 (1.96)	0.44	.645
(Trial 3)	11.55 (2.21)	11.30 (1.72)	11.25 (1.96)	0.18	.837
(Trial 4)	12.10 (2.27)	12.35 (1.60)	12.35 (1.66)	0.13	.877
(Trial 5)	12.45 (2.11)	12.75 (1.52)	13.20 (1.58)	1.17	.323
Total Trials 1-5	52.80 (8.94)	53.05 (6.75)	54.10 (6.23)	0.23	.795
(List B)	6.10 (2.00)	6.05 (1.64)	6.80 (1.94)	1.20	.313
(Trial 6)	11.15 (3.00)	11.15 (1.84)	11.40 (2.78)	1.53	.467 (FRD)
Recognition	13.40 (1.60)	13.70 (1.17)	14.20 (0.83)	3.21	.052
Supplementary AVLT indices					
Errors Trials 1-5	0.35 (0.93)	0.50 (0.69)	0.70 (1.08)	0.72	.496
Repetitions Trials 1-5	3.70 (3.18)	4.75 (3.46)	5.20 (2.73)	1.02	.369
Errors List B	0.45 (0.83)	0.30 (1.13)	0.25 (0.44)	1.08	.584 (FRD)
Errors Trial 6	0.20 (0.41)	0.00 (0.00)	0.20 (0.41)	1.20	.549 (FRD)

Table 7-9 (continued). Neuropsychological Test Scores (Mean and *SD*) by Group (CFS, Depressed, and Healthy)

Measure		CFS (n = 20)	Depressed (n = 20)	Healthy (n = 20)	ANOVA (df = 2,19) F	p-value
	Errors Recognition	0.50 (1.00)	0.60 (0.99)	0.85 (1.57)	0.70	.701 (FRD)
	% retention (T5-T6)	88.90 (14.90)	87.40 (9.65)	86.65 (20.22)	0.11	.899
	Learning index	6.50 (1.85)	6.40 (1.60)	5.90 (1.62)	0.75	.481
	30 minute recall List A	11.25 (3.23)	10.90 (2.99)	11.40 (2.66)	0.15	.859
	Errors 30 minute recall	0.20 (0.62)	0.55 (0.83)	0.50 (0.69)	2.80	.247 (FRD)
	Learning over trials	20.55 (7.16)	19.30 (5.57)	15.90 (6.65)	4.45	.018*
	Long-term % retention	91.55 (22.96)	84.40 (17.22)	86.85 (20.15)	0.73	.488
VDLT	(Trial 1)	4.15 (1.53)	4.15 (1.57)	4.40 (2.04)	0.15	.858
	(Trial 2)	6.45 (1.79)	6.60 (2.37)	6.70 (2.56)	0.08	.920
	(Trial 3)	7.50 (2.61)	7.65 (2.41)	7.85 (2.25)	0.17	.845
	(Trial 4)	8.40 (2.93)	8.50 (2.54)	8.85 (2.64)	0.38	.687
	(Trial 5)	9.30 (2.87)	8.90 (2.65)	9.45 (3.25)	0.32	.731
	Total Trials 1-5	35.80 (10.38)	35.80 (10.41)	37.30 (11.36)	0.25	.779
	Recognition	13.30 (0.92)	13.35 (1.31)	13.15 (1.87)	0.15	.864
Supplementary VDLT indices						
	Errors Trials 1-5	12.05 (6.82)	12.75 (6.84)	16.20 (11.05)	1.72	.193
	Errors Recognition	1.25 (0.97)	1.00 (0.97)	1.50 (1.10)	1.36	.268
	Learning index	5.70 (2.18)	5.25 (1.83)	5.65 (1.79)	0.41	.667
	30 minute recall	8.90 (2.57)	8.80 (2.55)	8.95 (3.39)	0.02	.981
	Errors 30 minute recall	2.65 (1.95)	2.80 (1.36)	3.05 (2.04)	0.37	.695
	Learning over trials	15.05 (7.27)	15.05 (7.09)	15.30 (5.40)	0.01	.989
	Long-term% retention	99.65 (25.45)	101.15 (22.12)	95.45 (25.90)	0.31	.733

See Chapter 6 (Methodology) for full explanation of the supplementary AVLT and VDLT indices.

* $p < .05$; [a] significantly different from CFS group ($p < .017$); (FRD) = Friedman two-way ANOVA.

ANOVA revealed a group difference on two of the neuropsychological tests (COWAT and Auditory-Verbal Learning Test) - see Figures 7-4 and 7-5.

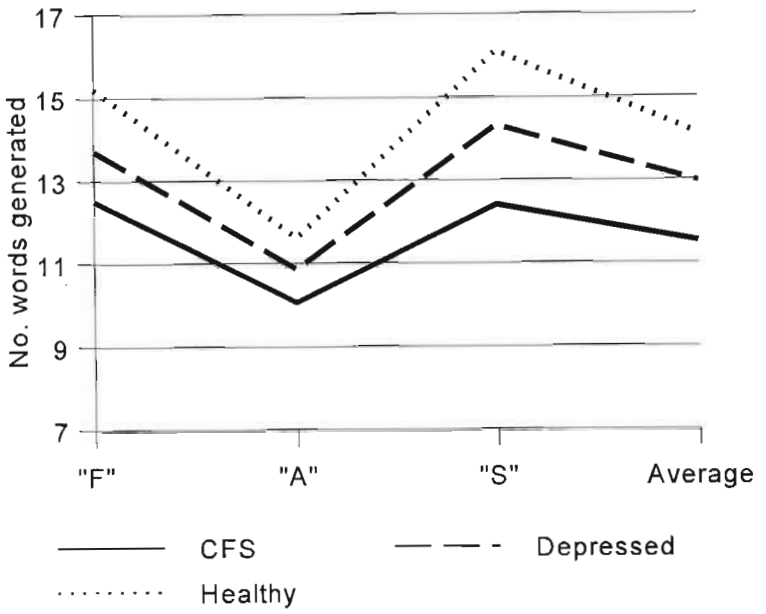

Figure 7-4. COWAT Profiles for CFS and Control Groups.

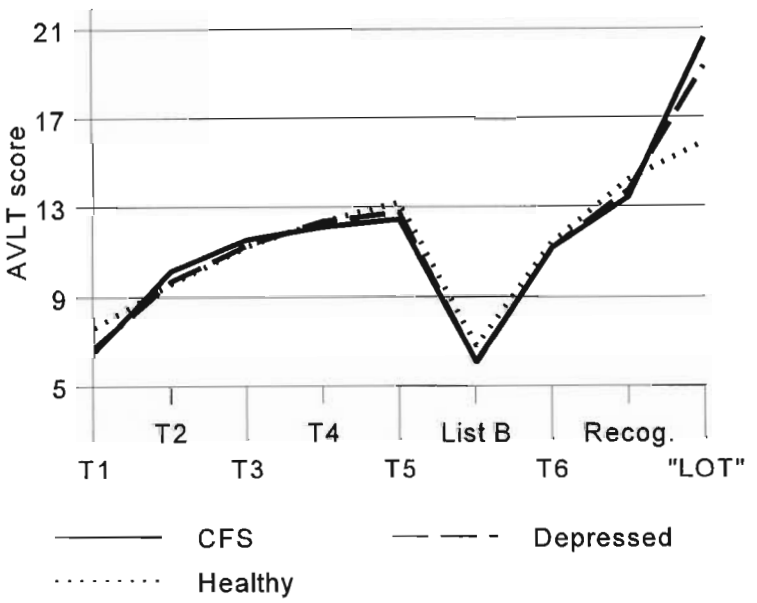

Figure 7-5. AVLT Profiles for CFS and Control Groups.

The variables showing these differences were, on the COWAT, the number of words generated by using the letter "S", and on the AVLT, the "learning over trials" or LOT index, and the number of words recalled on Trial 1. However, a series of post hoc *t*-test comparisons comparing CFS patients with the two control groups, found a difference between the CFS

patients and healthy controls on only one of these measures after application of the Bonferroni correction - COWAT "S" (t [38] = -2.68, p = .011). In contrast; the AVLT Trial 1 and LOT indices failed to reach significance at .017 (t [38] = -2.22, p = .033 and t [38] = 2.13, p = .040 respectively).

Three further ANOVAs were performed in order to assess possible group-by-trial variance on the three tests with repeated measures (i.e. PASAT, AVLT and VDLT). The PASAT is a test of increasing difficulty over trials, and so it is possible that group differences could emerge as a consequence of inter-trial variability. In order to assess this, the within-subject effect of trial, group, and group by trial interaction was examined in a repeated-measures MANOVA. As expected, subject performance on the PASAT decreased from Trials 1 to 4 (Hotellings F [3] = 56.83, p = .000); however, the rate of decline did not differ between the three groups (Hotellings F [3] = 0.28, p = .943) - see Figure 7-6. On the other hand, visual inspection of Figure 7-6 indicates that the CFS group performed consistently worse than the depressed and healthy controls. This appears to be a reasonably stable trend for most of the neuropsychological variables - see Chapter 8 for further discussion on this point.

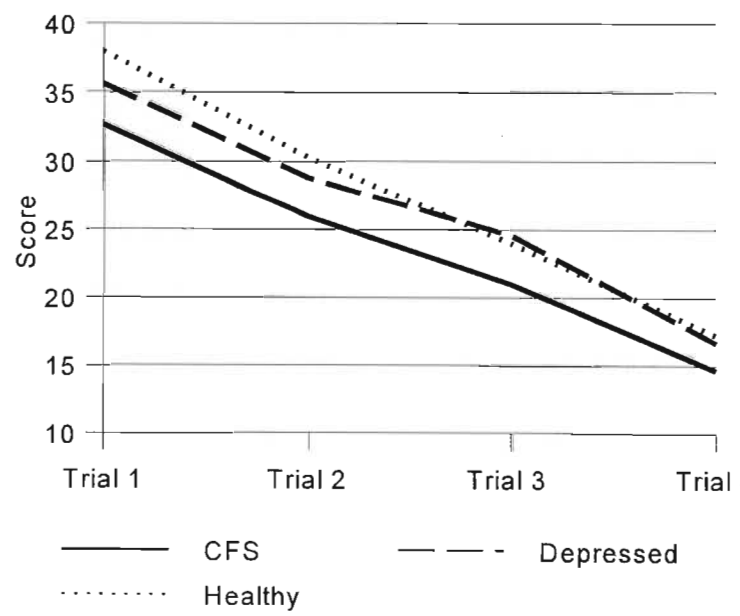

Figure 7-6. PASAT Performance Over Trials; CFS versus Control Groups.

Similar repeated-measures MANOVAs were conducted for the first five trials of the AVLT and VDLT (see Figures 7-7 and 7-8 below).

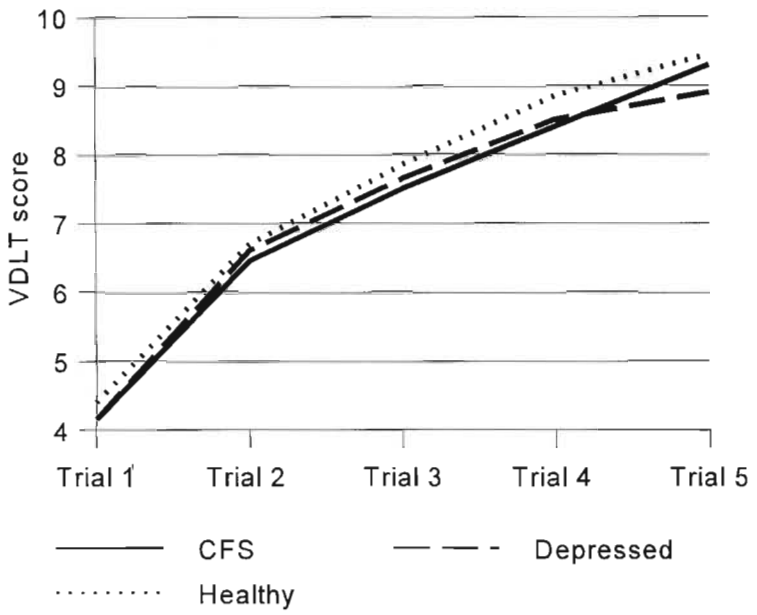

Figure 7-7. AVLT Performance Over Trials; CFS versus Control Groups

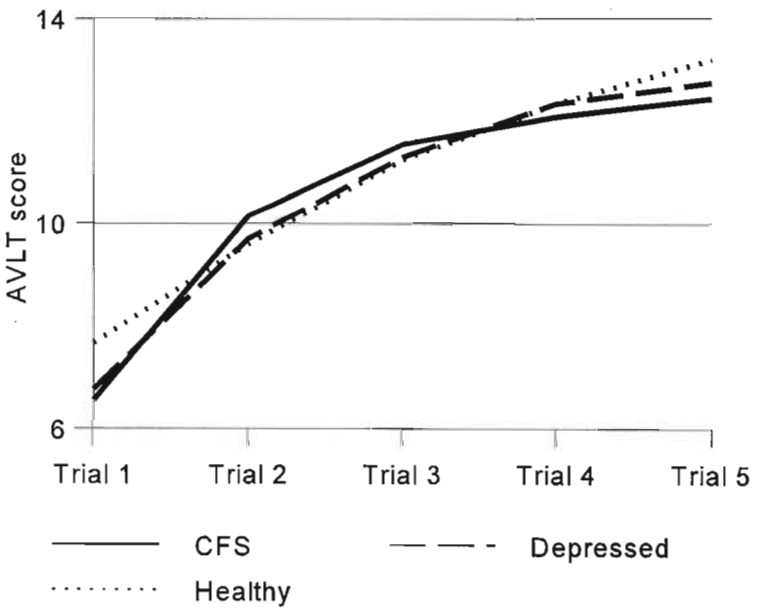

Figure 7-8. AVLT Performance Over Trials; CFS versus Control Groups.

Results again showed a significant trial effect (i.e. an increased number of items remembered on successive trials of both the AVLT (Hotellings F [4] = 153.55, p = .000), and VDLT (Hotellings F [4] = 82.79, p = .000). However, there was no significant group by trial interaction on either test (Hotellings F [8] = 1.17, p = .322; and Hotellings F [8] = 0.16, p = .996 respectively).

As mentioned earlier, both parametric and nonparametric analyses were performed on the neuropsychological data. The results of the nonparametric analyses were very similar; the only difference being that one further variable (SDMT - *Written*) demonstrated a group difference using the Friedman ANOVA (χ^2 [2] = 6.10, p = .047). However, a post-hoc analysis using a procedure for planned comparisons with the Friedman Model (Marascuilo & McSweeney, 1977) failed to identify the source of the difference (CFS/depressed comparison [ψ_1 = -0.05 ± 0.74]; CFS/healthy comparison [ψ_2 = -.070 ± 0.74]; and depressed/healthy comparison [ψ_3 = -.065 ± 0.74].

In order to assess the impact of depression on the three significant neuropsychological test findings (COWAT and AVLT), analysis of covariance (ANCOVA) was performed with the SCL-90-R depression raw score as the covariate. The significance of the group differences on all three neuropsychological measures disappeared when depression was entered as a covariate. This was an unexpected finding given that the SCL-90-R *Depression* score was not significantly correlated with any of the neuropsychological indices. On the other hand, depression was found to be significantly associated with the CFS Questionnaire *Total Score* (r = .51, p < .001) and the CFQ *Total Score* (r = .52, p < .001). Despite this association, there was no change in group significance levels when depression was entered as a covariate for the CFS Questionnaire *Total Score* (F [2,19] = 63.48, p = .000), and the CFQ *Total Score* (F [2,19] = 15.05, p = .000). In order to gain some clarity with respect to the distribution of depression-related impairment, correlations between the neuropsychological indices and SCL90-R *Depression* score were examined separately for each group. The spread of significant correlations was found to exist almost entirely for the depressed group, and for mainly one measure - the Visual Design Learning Test (see Table 7-10).

Table 7-10. Correlation Matrix Showing the Significant Associations Between the Neuropsychological Test Scores and SCL-90-R *Depression* Subscale (Raw Score)

	SCL-90-R *Depression* correlation by Group		
Neuropsychological Measure	CFS	Depressed	Healthy
Grooved Pegboard (preferred)	.52*	.14	-.20
VDLT (Trial 1)	-.02	.65*	.02
VDLT (Trial 2)	.01	.74**	.18
VDLT (Trial 3)	-.09	.62*	.00
VDLT (Trial 4)	-.13	.65*	.05
VDLT (Trial 5)	-.26	.54*	.07
VDLT (Total Trials 1-5)	-.13	.70**	-.22
VDLT (Recognition Trial)	-.39	.70**	.01
VDLT (Recognition Errors)	.10	-.66**	.18

* significant at p< .01; ** significant at p < .001

VDLT = Visual Design Learning Test

Finally, in order to exclude medication side-effects as a possible source of neuropsychological impairment in the CFS and Depressed groups, an additional ANCOVA was performed using the same three test indices (COWAT "S", and AVLT Trial 1 and Learning Over Trials) with medication as the covariate. There were no changes to the group significance levels (i.e. they remained significant at $p < .05$), suggesting that the observed neuropsychological differences could not be attributed to medication side-effects.

7.5 PREVALENCE OF NEUROPSYCHOLOGICAL IMPAIRMENT

Although ANOVA provides researchers with a useful technique for evaluating group differences, a more thorough assessment of individual case studies was seen as an important contribution to CFS research; to date only three studies (DeLuca et al., 1995; Krupp et al., 1994; and Michiels et al., 1996) have attempted to do this. Firstly, in order to assess the relative proportions of neuropsychological impairment, the test scores of each study participant were evaluated with reference to published normative data, and converted to standard scores (*z*-scores) - see disk file DESCRIPT.ZSC). Group representation across the various performance categories (following the classification system presented in Table 5-2, p.166) are presented in Figure 7-9.

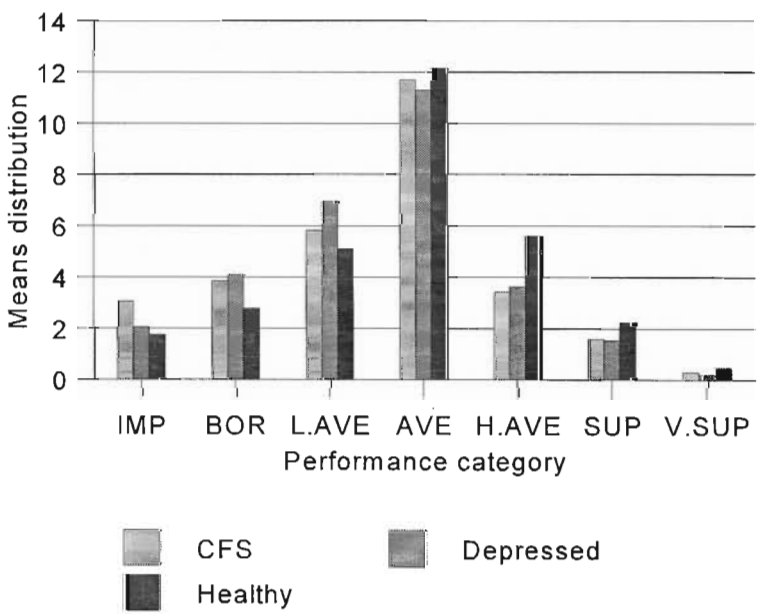

Figure 7-9. Distribution of Overall Neuropsychological Performance by Group (CFS, Depressed, Healthy).

This system of classification provides a useful model for clinical practice, although as mentioned earlier, the criterion for defining neuropsychological impairment varies from study to study. Generally speaking, impairment is defined in terms of score deviation from the mean, and clinical interpretation involves making neuropsychological sense of clusters of test score deviations. In contrast to the CFS and depressed subjects (see Figure 7-9), the healthy individuals appear to have fewer scores in the low average, borderline, and impaired categories, with a relatively greater representation of scores in the high average, superior and very superior categories. This trend was more formally examined using a method based on Krupp et al. (1994). In this procedure, a neuropsychological rating was defined and computed as follows: (1) *normal* - not more than one test score > 1.3 *SD*s below the mean; (2) *impaired* - two or more scores > 1.3 *SD*s below the mean. This represents a convenient cut-off for isolating borderline and impaired range *z*-scores, and also reduces the chance of making a false classification of impairment based on only one borderline or impaired score. In this respect, Lezak (1995) suggests that the presence of one discrepant score in an assessment can usually be explained as a chance deviation. Table 7-11 shows that while 40% of the control group fell within the normal range, only 10% of the depressed group, and 5% of the CFS attained a normal rating. In comparison to the healthy group, both the CFS and depressed groups displayed substantially more cases in the impaired category. Group differences were significant on statistical analysis (χ^2 [2] = 9.57, p = .008). Although there was no difference between the CFS and depressed groups (χ_1^2 [1] = 0.17, p >.05), the CFS/depressed versus healthy comparison was significant at the 95% confidence level (χ_2^2 [1] = 9.40, p < .05).

Table 7-11. Neuropsychological Ratings for CFS, Depressed and Healthy Subjects

	Number of subjects with impaired scores	
Group	Zero or one score > 1.3 *SD*s below mean (Normal)	Two or more scores >1.3 *SD*s below mean (Impaired)
CFS	1 (5%)	19 (95%)
Depressed	2 (10%)	18 (90%)
Healthy	8 (40%)	12 (60%)

In order to identify the source of the neuropsychological impairment, the frequency of normal versus impaired neuropsychological scores was analyzed using a classification system based on Skoraszewski et al. (1991); the only difference being that a more conservative 1.3 *SD* cut-off was used in contrast to the 1 *SD* used by Skoraszewski and colleagues. Specifically, a score was defined as *impaired* if it exceeded 1.3 *SD*s from the published mean for that test, and *normal* if it fell within 1.3 *SD*s from the published mean. None of the neuropsychological variables reached significance; the closest to approach significance was Trial 2 of the PASAT ($\chi^2 = 5.02, p = .081$).

An impairment rating (IR), similar to that used by DeLuca et al. (1995) was also derived from the *z*-score data. An IR of 0 was assigned to individuals who obtained neuropsychological test scores within 1 *SD* of the representative (i.e. age and sex) published norms; scores between 1 and 2 *SD*s below the norms were assigned a rating of 1; scores between 2 and 3 *SD*s below the norms were assigned an IR of 2; and scores greater than 3 *SD*s received an IR of 3. Once raw scores had been transformed into *z*-scores,[52] the IR's were then added to obtain a summary impairment rating (SIR) reflecting the overall performance of each subject (see Figure 7-10). The final SIR score was used as the dependent variable for a two way ANOVA contrasting the CFS, depressed and healthy groups. Results revealed a significant group difference ($F\,[2,19] = 4.22$, $p = .003$); however, *t*-test comparisons were non-significant after controlling for multiple experiment effect (CFS/healthy comparison; $t\,[38] = 2.10$, $p = .042$). Nevertheless, a trend of comparatively greater impairment moving from the healthy group, through depressed subjects to the CFS group, is apparent from visual inspection of Figure 7-10.

52

Normative data representing the age extremes of the subjects used in this study, does not exist for all of the measures used. Test scores omitted from this analysis included: COWAT (average score, and individual trials for 8 of the 20 triplets); AVLT and VDLT (all supplementary indices except AVLT 30 minute recall); errors on the TMT and SDMT; and PASAT (Total Score). The PASAT trials of the 13 year old subjects were evaluated using the norms for 16-19 year olds'.

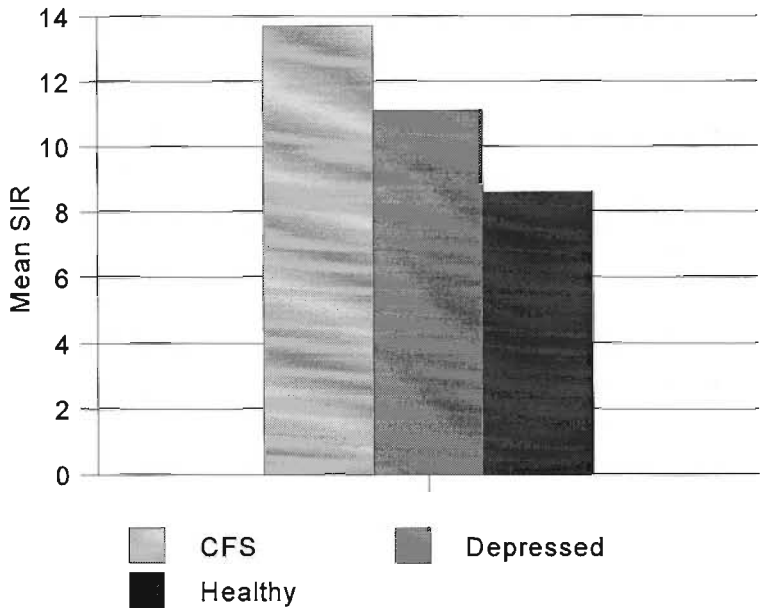

Figure 7-10. Mean Neuropsychological Summary Impairment Ratings (SIR) for CFS and Control Groups.

CHAPTER 8

DISCUSSION AND CONCLUSION

8.1 PSYCHOLOGICAL FINDINGS

8.1.1 CFS symptomatology

Although the Intake Questionnaire (see Table 7-1) was not subjected to statistical analysis, it is clear from the frequency distribution of symptom endorsement that individuals with CFS differ from both the depressed and healthy individuals. Apart from the expected findings of greater mental and physical fatigue in CFS patients, it is apparent that they also rate the impact of fatigue in a more negative way (i.e. as having relatively greater negative impact on occupational, social, and recreational functioning). Myalgia, a characteristic feature of CFS, was endorsed by the majority of CFS patients (95%) and by two individuals (10%) in the depressed group. These findings are compatible with those reported in the literature; for example, Abbey and Garfinkel (1991) report that aching muscles (i.e. myalgia) may be seen in as many as 30% of depressed individuals, while fatigue is listed as one of the associated features of the DSM-III-R criteria for depression (APA, 1987). It is interesting to note that one of the healthy subjects (case 52) admitted to the presence of myalgia; however, this endorsement was compatible with her occupation (physiotherapist), and enquiry revealed acknowledgement of muscle pain from time to time. All of the CFS patients reported sleep disturbance, compared with 90% of depressed individuals and 25% of the healthy controls; this finding is comparable with studies that have found a high incidence of sleep disturbance in both CFS and depressed individuals (Abbey & Garfinkel, 1991; Buchwald et al., 1994; Komaroff, 1993). In examining the incidence and severity of mood disturbance, it is evident that compared to the healthy controls, both the CFS and depressed patients perceive themselves to be more compromised across a range of psychological symptoms (i.e. depression, loss of pleasure, anxiety, mood changeability, and irritability). Similar psychological profiles in CFS and depression studies have been reported by Abbey and Garfinkel (1991) and Komaroff (1993).

With regard to the CFS Symptom Checklist, the current findings indicate that individuals diagnosed with CFS endorse a significantly greater range of symptomatology than either healthy individuals or patients with major depression. This tendency for CFS patients to complain of "almost everything" when completing symptom checklists has been commented on previously (Katon & Walker, 1993), and represents abnormal illness behaviour. Checklist items with seemingly high discriminative ability included: spatial disorientation, fainting spells (blackouts), fever, intolerance of bright lights and alcohol, outbreak of fever blisters, painful lymph nodes, and muscle/joint aches; all of these have previously been mentioned as important in the differentiation of CFS and depression (Bell, 1994; Komaroff, 1993). Also in line with previous research (e.g. Abbey & Garfinkel, 1991) is the finding of substantial symptom overlap between the CFS and depressed patients. Common symptoms included: physical and mental fatigue, mood lability, depression, and neuropsychological dysfunction (e.g. attentional and memory difficulties). In comparison to other studies using similar symptom checklists (e.g. Smith et al., 1993), a slightly higher endorsement rate in the current sample of CFS patients was evident for some symptoms (e.g. depression, light sensitivity, sleep disturbance, and joint pain).

8.1.2 Cognitive Failures Questionnaire (CFQ)

Results from the CFQ indicated that relative to depressed and healthy individuals, CFS patients complain of a wide range of neurocognitive problems encountered in everyday life. These findings are consistent with those of Smith et al. (1993). In a discriminant function analysis that gave an overall correct classification of 75%, both memory difficulties and visuospatial deficits were found to lie at the source of the most discriminating items. Although not impaired to the same degree as the CFS patients, the depressed individuals were found to have a significantly higher level of cognitive failure relative to the healthy controls. Again, neurocognitive difficulties are a recognized component of major depression (Cohen et al., 1982).

Reported neuropsychological correlates of the CFQ appear to be in short supply. Broadbent et al. (1982) suggested a lack of association with word recall in adults, but a positive correlation with cognitive measures in children (counting backwards and mirror tracing task). In

the current study, the CFQ *Total Score* was not associated with any of the neuropsychological measures, but showed a high correlation with the symptom dimensions of the SCL-90-R. The highest correlation (.78, $p < .001$), was found to be with the *Obsessive-Compulsive* subscale; in the writer's clinical experience, these SCL-90-R items are typically endorsed by individuals with neuropsychological deficits as well as those with overt obsessive-compulsive symptoms. The former report memory and concentration problems, having to work slowly to ensure correctness, and having to double-check behavioural output. While "normal" functioning on the CFQ has not yet been defined in terms of a range or cut-off score, the results of the current study (like those of Smith et al., 1993) indicate that it is apparently normal to experience mild or transient neuropsychological dysfunction. Since these kinds of self-rating scales appear to be gaining in popularity in the neuropsychological literature (Knight & Godfrey, 1995), further work on the discriminative ability of the CFQ seems warranted.

8.1.3 Symptom Checklist 90-R(evised) (SCL-90-R)

Significant group differences were evident on the SCL-90-R, with the CFS patients manifesting a greater degree of psychopathology than the healthy controls. This difference was evident across the whole spectrum of SCL-90-R symptom dimensions, suggesting that CFS-related psychological symptomatology is wide-ranging. This broad-based impairment was also found by Valdini, Steinhardt and Feldman (1989), and Vercoulen et al. (1994) who used the original version of the SCL-90. Like Valadini and colleagues, subscale elevations on *Depression* and *Obsessive-Compulsive* were amongst the highest, although in contrast to their study, the current study findings revealed *Somatization* to have the highest elevation. The four highest subscale elevations in the current study (*Somatization, Obsessive-Compulsive, Depression, and Anxiety*) are identical to the four highest subscales found by Egle et al. (1996) in their investigation of 40 German CFS patients. Apart from giving some external validation of the group selection criteria used in the current study, the overall profile similarities add support to the view that CFS is a heterogeneous condition characterized by multiple psychological symptoms. In a DFA, the *Somatization* and *Depression* subscales, along with *Phobic Anxiety* and *Hostility*, were found to contribute to a correct group classification rate of 82%.

The SCL-90-R profiles of the CFS and depressed groups are noteworthy for their similarity rather than their differences, indicating a high degree of symptom overlap for these conditions. In addition, both groups showed an equal number (i.e. 80%) of "positive" cases defined by two subscale elevations above $T = 63$, or a $GSI \geq 63$. This is somewhat higher than the figures reported by Mathew et al. (1991) in their study of 35 fatigued EBV patients (44%), and 35 fatigued non-EBV controls (52%). Additional comparative figures are not reported for other CFS studies using the SCL-90-R, although Schweitzer et al. (1994) found that 67% of their CFS patients scored above the cut-off for psychiatric morbidity using the General Health Questionnaire. As might be anticipated, the *Depression* subscale was the highest peak in the SCL-90-R profile of the depressed subjects; however, this was accompanied by elevations on other subscales (especially *Obsessive-Compulsive, Interpersonal Sensitivity,* and *Anxiety*). This heterogeneity of symptoms in depression is well-recognized in the psychiatric literature (Thase, 1991). Interestingly, the saw-toothed configuration of the SCL-90-R depressed group profile evident in the current study, is virtually identical to the profile of the 148 depressed subjects presented by Weissman (1977); this similarity suggests that the depressed controls used in the current study are reasonably representative of the depressed psychiatric population. The results of the SCL-90-R *Depression* subscale also indicated some variation (in terms of symptom severity) within the depressed group. A frequency distribution of cases revealed major depression in approximately half of the sample (nine individuals), while the balance were presumably comprised of less severe depression and dysthymia. An unexpected finding was that one of the apparently healthy subjects (Case 52) scored above $T = 70$ on the *Depression* subscale; as discussed below, this individual reported being stressed at the time of assessment, and this could have accounted for the general elevation of his SCL-90-R protocol.

Only two of the nine subscales (*Somatization* and *Obsessive-Compulsive)* were found to differentiate CFS from depressed patients. A preoccupation with bodily complaints and somatic concern in both individuals with CFS, and depression, is well-documented in the literature (Manu, Lane & Mathews, 1989; Mathews, Manu & Lane, 1988; Schweitzer et al., 1994; Thase, 1991). However, the results of this study suggest that somatic dysfunction is more pronounced in CFS patients. Although the finding of prominent obsessive-compulsive symptoms in CFS individuals has been noted using the SCL-90-R (Egle et al., 1996), its significance as a differentiating

characteristic between CFS and depression has not been previously documented. While obsessive-compulsive behaviour and personality features may well be a feature of the broad-based psychopathology associated with CFS, this has tended not to be a feature of studies using relevant investigative techniques (Kruesi et al., 1989; Millon et al., 1989; Pepper et al., 1993). Moreover, it is important to acknowledge (as mentioned previously), that endorsement of the items making up the *Obsessive-Compulsive* subscale could also represent an acknowledgement of subtle neuropsychological dysfunction. To this extent, it is possible that the SCL-90-R findings reflect a tendency for CFS and depressed individuals to be differentiated by progressively dysfunctional neuropsychological symptoms.

The finding that four healthy subjects (25%) fulfilled the criteria for "caseness" on the SCL-90-R requires comment. Derogatis (1983) reported a "hit-rate" of 85-87% for mixed cohorts used in the test development; however, as he points out, the base rate for psychiatric disorder in other samples could be different. Unfortunately, the validity of the operational rule for caseness in a South African population is unknown, although looking at the profile of the healthy sample used in this study, all of the subscales fell within 10 *T*-score points of the mean (40th - 60th percentile) suggesting that the scaling is reasonably reliable. Although the presence of four positive cases is probably acceptable in terms of base rate limits, these "healthy" subjects were individually examined (subscale *T*- scores appear in parentheses). The youngest of these (Case 58 - female aged 23 years) had a *GSI* = 65 and elevations on the *Obsessive-Compulsive* (71), *Psychoticism* (73), *Interpersonal Sensitivity* (66), *Depression* (66), and *Anxiety* (66) subscales. Case 45 (female aged 34 years) had a *GSI* = 68 with accompanying elevations on *Somatization* (66), *Obsessive-Compulsive* (72), *Depression* (70), and *Hostility* (74). Case 55 (female aged 41 years) had marginal elevations on 3 subscales: *Obsessive-Compulsive* (64); *Paranoid Ideation* (63); and *Psychoticism* (64). All of these individuals reported feeling mildly fatigued, while two subjects (cases 45 and 55) acknowledged the recent experience of mild or moderate mood disturbance. The last case (Case 42 - male aged 50) was a medical specialist who indicated that he was under temporary but considerable work stress at the time of evaluation. Accordingly, he showed a *GSI* = 74 and subscale elevations on *Obsessive-Compulsive* (66), *Interpersonal Sensitivity* (73), *Depression* (76), *Anxiety* (64), *Hostility* (79), *Paranoid Ideation* (77), and *Psychoticism* (79).

8.2 NEUROPSYCHOLOGICAL FINDINGS

8.2.1 Group Comparisons Using ANOVA

Results of the neuropsychological assessment revealed group differences for three of the seven tests used in this study. Specific test indices showing this difference were the "S" trial of the Controlled Oral Word Association Test (COWAT), the *Written* administration of the Symbol Digit Modalities Test, and in the Auditory Verbal Learning Test, the number of words recalled on Trial 1 and the "learning over trials" index (a measure of learning efficiency). In all instances, a trend of relatively greater dysfunction was evident in the test scores moving from the healthy group, through the depressed controls, to the CFS patients. Although this trend was a fairly common feature of the overall neuropsychological test data (65% of the test scores followed this pattern), visual inspection of the data indicates that the magnitude of the inter-group score differences is modest. Consequently, post hoc analyses (with correction for multiple experiment effect), failed to identify the source of the group difference in all instances except the COWAT, where healthy individuals were able to generate more words beginning with the letter "S" than the CFS group. This situation is not unheard of in data analysis (Everitt, 1996), although it does make the interpretation of the data less straightforward. On the one hand, it may have to acknowledged that the observed differences in this study are artifactual and a consequence of multiple experiment effect (Type 1 error). However, Everitt maintains that multiple comparison tests tend to err on the conservative side, thereby diminishing legitimate group differences.

In consolidating these differing viewpoints, it is probably wisest to conclude that a significant group difference was evident only one measure, the COWAT. As such, the evidence for prominent neuropsychological impairment in CFS was not convincingly demonstrated on univariate *F*-test group comparisons. Similar findings of subtle neuropsychological impairment in CFS are reported by Riccio et al. (1992) who found evidence of impairment in only one of seven tests (Wechsler Memory Scale), and Krupp et al. (1994) who found CFS-related impairment in only one of nine tests (*Digit Symbol*). In contrast, Schmaling et al. (1994) failed to find any measures in their test battery of six tests that discriminated CFS from the healthy controls, while Altay et al. (1990) found that their sample of CFS patients outperformed age-

matched controls on the majority of neuropsychological measures.

In accepting the COWAT result as an index of a true group difference, what does this tell us about the nature of the neuropsychological difficulties experienced by CFS patients? As mentioned previously, the COWAT is regarded as a sensitive measure of brain dysfunction, however low scores may be associated with a variety of pathologies (e.g. frontal lesions, dementia, and Parkinson's disease). In terms of underlying neuropsychological processes, low scores tend to be associated with mental inflexibility, impaired semantic processing and memory dysfunction (Lezak, 1995). Given that all of these functions have been implicated in CFS, it is unclear which process or combination of processes is responsible for the current result. In the four CFS studies that have employed this measure, there were no differences between CFS patients and controls (Cope et al., 1995; Grafman et al., 1993; Krupp et al., 1994; and Riccio et al., 1992). In terms of its association with other variables used in this study, the COWAT "S" trial was modestly correlated with only two other neuropsychological variables (errors on Part B of the Trail Making Test, $r = .53, p < .01$; and the recognition trial of the VDLT, $r = .56, p < .01$). Informed by clinical experience in using this test across a wide spectrum of neuropathology, the writer is of the opinion that of the three COWAT trials, most subjects find the "S" trial easiest, an impression that is supported by the slightly higher scores obtained on this trial in normative studies (Spreen & Strauss, 1991). For this reason, most subjects obtain higher scores on the "S" trial than on the preceding trials; this was not the case for the CFS subjects used in the current study. In terms of an explanation, it is possible that in CFS patients, pronounced fatigue or exhaustion sets in by the third trial and they "run out of steam", figuratively speaking. Stated differently, cerebral resources maybe depleted more quickly in CFS patients when compared to healthy controls. An alternative and possibly related hypothesis, is that the COWAT findings represent evidence of discrete neuropsychological dysfunction (i.e. an executive deficit). King and Caine (1995) review evidence suggesting that HPA activity is associated with selective information processing. In this respect, it is possible that CFS patients experience a difficulty in distinguishing relevant from irrelevant information, and that this is related to the HPA dysregulation hypothesized to lie at the source of CFS symptomatology. Executive deficits have generally not been a feature of those neuropsychological investigations that have employed appropriate measures (e.g. DeLuca et al, 1995; Krupp et al., 1994; Schmaling et al., 1994).

Nevertheless, of relevance here would be the finding by Schwartz et al. (1994) of frontotemporal abnormalities in both CFS and depressed patients using SPECT. An argument against this possibility in the current study is that the CFS and depressed patients performed adequately on the first two trials of the COWAT (frontotemporal abnormalities might be expected to exert a consistent effect over all three trials). A counter-argument to this suggestion is that inconsistent performance could represent an attentional fluctuation; in a response generation task like the COWAT, executive and attentional control mechanisms are operational (Cohen, 1993). Recent conceptual views of attention suggest that disturbances in the brain's arousal and attentional mechanisms could lead to fatigue, distractibility and inconsistent test performance (Cohen 1993; van Zomeren & Brouwer, 1994). The possibility that fatigue could account for the observed result is supported by Cohen and Sparling-Cohen (1993) who comment that "fatigue is a response tendency, one in which an individual shows an inability to sustain continued performance" (p.72). Unfortunately, it is difficult to isolate the underlying deficit; van Zomeren and Brouwer conclude that "it seems that we must accept the fact that fatigue, motivation, and attention are intertwined in such a way that it is often impossible to separate them" (p. 165). Whatever the cause, the manifestation is likely to be seen on tasks that require effortful cognitive processing; support for this contention comes from recent investigations of CFS (DeLuca et al., 1995; Michiels et al., 1996). In contrast to recent investigations, the current study failed to demonstrate evidence of impaired memory or slowed speed of cognitive processing (DeLuca et al., 1995; Marshall et al., 1997). However, these deficits were not found in studies by Schmaling et al. (1994) and Cope et al. (1995).

A further finding of this study was the lack of association between levels of perceived mental fatigue and neuropsychological profiles. Both the CFS and depressed groups admitted to higher levels of mental fatigue in the intake questionnaire, yet this was significantly related to only one neuropsychological variable in the depressed group (errors/intrusions on List B recall of the AVLT, $r = .54, p < .01$). A similar lack of prediction was evident for the CFQ, where there were no significant correlations with any of the neuropsychological variables in the CFS group. It may therefore be concluded that subjective endorsement of mental fatigue in CFS patients is not a good predictor of objective neuropsychological deficit. A similar discrepancy between subjective and objective neuropsychological findings in CFS studies has been widely

acknowledged (Altay et al., 1990; Cope et al., 1995; DeLuca et al., 1995; Ray et al., 1993). There could be a number of reasons for this discrepancy. The first possibility is that compared to objective neuropsychological testing, questionnaires of subjective symptom endorsement are more sensitive to functional "colouration". For example, it is possible that perceptions of disability in CFS patients reflects a type of confirmatory bias (i.e. where there is symptom endorsement of symptoms that looks vaguely disabling); this would give validation to perceptions of sickness/disability. Neuropsychological tests are somewhat less vulnerable to this tendency, although they could be subject to the same influence if the subject chose to give up or put in less effort; such motivational distortion should however be easily recognized by a skilled examiner. Motivational distortion was not an observable feature of the current study except possibly on the last trial of the PASAT, where a handful of subjects (from all three groups) found that the demands of the test situation outstripped their resources, and they tended to give up. The point being made here is that while the neuropsychological test format offered ample opportunity for CFS patients to convince the examiner of cognitive dysfunction, this was not detected in any of the 60 subjects who all appeared to consistently give their best performance. To some extent, this observation would be compatible with reports that far from attempting to portray their dysfunction, CFS patients usually expect to perform well on neuropsychological tests (e.g. Sandman et al., 1993).

Ray et al. (1993) question the ecological validity of neuropsychological tests, indicating that this may account for a discrepancy between subjective and objective neuropsychological findings in CFS studies. Specifically, they suggest that neuropsychological tests represent cognitive abilities that may be removed from the realities of everyday life; this is in contrast to questionnaires that tap more directly into real life events. They argue that neuropsychological tests require a greater degree of effortful processing, and that a compensatory effort must be made to counteract inefficiency and possible fatigue. As a consequence of this need for increased effort, CFS patients may gain the impression that they have performed worse than they actually have (a perception not substantiated by objective test findings). Similarly, McDonald et al. (1993) and Marshall et al. (1997) found that although CFS patients may experience problems at the level of task initiation, they function adequately once they are "up and running". However, this observation lies in contrast to the current findings that CFS patients show performance

declines after reaching a satisfactory level of neuropsychological functioning.

Could depression account for the observed group difference in neuropsychological functioning? Because of the high incidence of depression in CFS patients and its potential effect on cognition, this question has been addressed by virtually all CFS studies that have investigated neuropsychological functioning. The majority have suggested that observed neuropsychological functioning could not be attributed to depression (DeLuca et al., 1993; McDonald et al., 1993; Michiels et al., 1996; Riccio et al., 1992; Sandman et al., 1993; Schmaling et al., 1994;). However, in the current study, the group differences on the COWAT disappeared when depression was entered as a covariate, suggesting that depression accounted for the observed result. A similar finding was obtained by Marshall et al. (1997), although they argued that the magnitude of depression (based on a high/low split of the CFS group), accounted for only a minority of the measures, and for none of what they considered to be important indices (i.e. direct measures of speed of cognitive processing). In an attempt to understand more fully the relationship of depression to neuropsychological functioning in the current study, correlations of the SCL-90-R *Depression* raw score with the various test indices were examined. Results indicated that the association between depression and neuropsychological functioning was confined almost entirely to the depressed patients; in the CFS group there was only one positive correlation on a non-cognitive measure (Grooved Pegboard). Interestingly, those test indices related to the *Depression* raw score were confined entirely to one test (VDLT), suggesting that in the current study, the effect of depression on neuropsychological functioning was restricted to non-verbal memory. This is consistent with the literature on depression; Cassens and colleagues (as cited in Hinkin et al., 1992) found that higher-order attention (especially for visual stimuli) was detrimentally affected by depression. The current results are also consistent with the emerging view that depression may be associated with right-sided cerebral dysfunction (King & Caine, 1995). Feedback from subjects (not specific to any particular group) during administration of the VDLT, indicated that they found it to be a challenging task with some complaining of stimulus overload. It could be argued that the VDLT required a greater recruitment of cerebral resources (i.e. a higher degree of effortful processing), and that a deficit in this function was maximal for the depressed subjects.

To summarise thus far, the study findings support the idea of impaired effortful cognitive processing in CFS, although the exact source of the impairment is unclear. While the neuropsychological profiles of the CFS and depressed individuals do not differ on univariate testing, a trend of relatively greater impairment in the CFS group is evident when test scores are compared across the three groups (see Table 7-9). In addition, there is evidence that CFS and depressed individuals are differentially affected by depressive symptomatology and concurrent mental fatigue. More specifically, while the SCL-90-R indicated that there were no group differences in terms of depressive symptomatology, the impact of depression was more directly correlated with neuropsychological function in the depressed group than for the CFS patients (see Table 7-10). One can only speculate on the significance of this finding, however it could indicate that although CFS patients perceive themselves to be depressed, the experience of their depression is qualitatively different to that experienced by clinically-diagnosed depressed individuals. One problem of establishing causality is that the SCL-90-R *Depression* subscale includes items that could have overlap with a range of psychological conditions (including stress and fatigue). In other words, it is possible that CFS patients obtain similar scores to depressed patients not because they manifest similar levels of depression, but because they experience greater fatigue. This hypothesis was supported by an informal comparison of responses to *Item 14* of the SCL-90-R (*Feeling low in energy or slowed down)*, where respective group means were CFS (3.10), Depression (1.80), and Healthy (1.00). Similarly, respective group means of *Item 71* (*Feeling everything is an effort*) were CFS (2.65), Depression (2.20), and Healthy (0.35).

8.2.2 Neuropsychological Impairment Ratings

The results of a more clinical evaluation of neuropsychological performance in which test scores were converted to *z*-scores and classified as either normal or impaired, revealed similar trends to the univariate analysis; that is, a trend of relatively greater neuropsychological impairment in moving from the healthy, through the depressed, to the CFS subjects. Again, similar levels of impairment were evident for individuals in the CFS and depressed groups (95% and 90% respectively); this contrasts with 60% of the healthy individuals. This classification was

statistically significant for the CFS and healthy comparison. A similar statistical result (in terms of direction) was obtained in the clinical impairment ratings of Krupp et al., (1994), although the classification figures in their study were different (35% of the CFS group were impaired compared to 5% of the healthy controls). It is problematic to make a direct comparison to the Krupp et al., (1994) study given the varying methodology and different comparison standard used by Krupp and her colleagues. Specifically, while the current study scores were referenced against published norms and used a 1.3*SD* as opposed to a 1*SD* cut-off, Krupp et al. used an estimated premorbid level of ability (based on the reading portion of the Wide Range Achievement Test-revised, and the WAIS-R Information and Vocabulary subtests), against which to evaluate the scores of their study subjects. It may be that these different referencing methods account for a differential sensitivity of the impairment ratings used here and in the Krupp study. Although not applied to a CFS population, the clinical impairment rating used by Skoraszewski et al. (1991) was closer in format to the one used in the current study; unfortunately they did not employ a control group of healthy individuals, and so a direct comparison of classification rates cannot be made.

The fact that 60% of the healthy subjects in the current study were rated as impaired requires comment. A possible criticism might be that the criterion for defining impairment (i.e. one test score in the borderline or impaired range) is too sensitive, with the consequence that it produces too many false positives. However, in clinical practice, the presence of a borderline or impaired score in an otherwise healthy protocol should alert the examiner to the idea that all may not be well; at the very least, it would warrant explanation and further assessment. It is difficult to be prescriptive on this point, given acceptable variations in the definition of neuropsychological impairment in research and in practice. It might however be noted that the *z*-score cut-off of 1.3 *SD*s used in the current study is more conservative than the 1 *SD* used by Skorazewski et al. (1991). An additional explanation for the high incidence of impairment might lie in the unrepresentative nature of the published norms to establish *z*-scores; this could create a bias towards impairment in certain instances. For example, the PASAT norms used in the current study do not extend down to 13 years (the age of the youngest participants in the current study); and are not stratified for education. This could increase the risk of being classified as impaired in certain cases. Additionally, in terms of the criterion of impairment used in the current study,

intra-individual variability in test scores (in conjunction with a cut-off point), could create a situation whereby it might be easier to be classified as impaired as opposed to normal (i.e. the window of classification is much larger for the impaired rating than it is for the normal rating). Since the source of neuropsychological impairment (i.e. in terms of test) could not be determined using the same cut-off (1.3 *SD*) in a χ^2 distribution analysis, the neuropsychological protocols were individually examined. There were however no obvious patterns or clusters of impaired scores in the data, except that the VDLT appeared to be over-represented in terms of borderline or impaired scores. One individual (Case 51 - female aged 46) had impaired scores (eight in total) on five of the seven neuropsychological tests. There is no easy explanation for this finding; she was reportedly in good health and presented with an absence of risk factors or history that could account for the impairment. The absence of any scores above $T \geq 63$ on the SCL-90-R also argues against an explanation based on psychopathology. The fact that such individuals may be encountered and mis-classified by neuropsychologists, underscores the importance of acknowledging the limitations of the neuropsychological paradigm.

Given the profile similarities between the CFS and depressed individuals, is it possible that these two disorders share common etiologic mechanisms? Two lines of investigation (SPECT and immunological studies) appear to give somewhat conflicting answers to this question. As indicated earlier in this discussion, SPECT abnormalities have been found in the frontotemporal brain areas of CFS and depressed individuals (Schwartz et al., 1994a, 1994b). Schwartz and colleagues have hypothesized that the observed SPECT abnormalities could be associated with cellular dysfunction caused by circulating cytokines. Some support for this view comes from the finding that interferon-induced fatigue appears to principally interfere with frontal lobe cognitive functioning (Adams et al., 1984). This latter finding needs to be considered within the broader framework of altered immunity and neuroendocrine abnormalities which have been associated with CFS and depression (Demitrack, 1994; Goldstein, 1993). In this respect, HPA dysfunction occurs in both conditions (Wessely, 1993). However, despite the apparent similarities between CFS and depression, there is also some evidence that these conditions have unique SPECT profiles. For example, Costa et al. (1995) found that the degree of brainstem hypoperfusion was significantly greater in their CFS patients. Schwartz et al. (1994b) also indicated some discriminating features between these patient groups (in terms of a midcerebral

uptake index), suggesting that the particular pattern of blood flow abnormalities observed in their CFS subjects, was most likely due to a viral-induced vascular pathology.

In consolidating these findings, it seems reasonable to conclude that there are some grounds for viewing CFS and depression as neurophysiologically distinct conditions. This being the case, why were the neuropsychological measures used in the current not more discriminating? There does not seem to be an clear explanation for this. One possible answer lies in the composition of the CFS sample used in this study, in that the average patient may have progressed too far along the recovery phase of the illness. Some support for hypothesis comes from the improvement rating which the CFS patients completed in the Intake Questionnaire; the average improvement rating was found to be 49.8% (range 0 - 80). Perhaps a greater degree of neuropsychological dysfunction may have been evident in CFS patients with more acute symptomatology. Subject heterogeneity could therefore have been a confounding variable.

CONCLUSION

In addressing the hypotheses set out in Chapter 5, the following conclusions are reached:

(1) Neuropsychological difficulties are detectable in individuals diagnosed with CFS although the level of dysfunction is very subtle, and is of a magnitude and scope that is unlikely to significantly interfere with routine daily cognitive functioning. The nature of the difficulty can be understood as an executive dysfunction, and more specifically as a failure in response generation. The exact source of the difficulty is unclear, since it could encompass elements of fatigue and/or a deficit in supervisory attentional control. What can be stated with greater confidence, is that it is most likely to be manifested in tasks requiring effortful cognitive processing or selective information processing. To this extent, it is evident that CFS patients function perfectly adequately up to a point, but are prone to greater mental fatigue than either depressed or healthy individuals. Depression and potential medication side-effects were ruled out as possible sources of the dysfunction.

(2) There were no discernible differences in the overall neuropsychological test profiles of the CFS and depressed individuals. Nevertheless, a trend of declining neuropsychological test performance was evident in moving across the spectrum of healthy, depressed, and CFS individuals used in this study (i.e. the CFS group appeared to perform less efficiently on the neuropsychological tasks than the depressed and healthy individuals). However, a significant group difference was evident only when the CFS and healthy individuals were compared. Although the magnitude of neuropsychological difficulty for CFS and depressed patients is similar, there were indications from the test data that the experience of depression may have a differential impact on neuropsychological functioning in these two groups.

(3) The psychological profiles of CFS and depressed individuals are remarkably similar in terms of levels of reported psychological distress. Distinguishing features are

significantly higher levels of somatization and obsessive-compulsive tendencies in CFS; the latter may be a manifestation of perceived cognitive failure. Given these differences, the current study does not support the idea that CFS is a depressive variant.

(4) There appears to be a discrepancy between reported levels of subjective cognitive failure and objective neuropsychological findings in patients with CFS. Since this has also been consistently reported in other CFS studies, it would appear to be a characteristic feature of CFS.

(5) The limitations of the neuropsychological paradigm as an adjunct to the diagnosis and treatment of CFS are apparent. Firstly, it seems unlikely that, given the subtle nature of the dysfunction and marked inter-study variability, neuropsychological cut-off scores or profile analysis will assist the identification of CFS. Secondly, the type of deficit observed in this study is not specific to CFS, since depressed individuals had very similar profiles. Although the rating of individual cases as normal or impaired was successful in discriminating the CFS from the healthy subjects, a high level of false positives in the healthy group limits the applicability of this diagnostic method. Notwithstanding these criticisms however, neuropsychological assessment remains a potentially useful investigative tool in CFS research.

LIMITATIONS OF THE CURRENT STUDY AND SUGGESTIONS FOR FUTURE RESEARCH

This study has a number of limitations which need to be specified. Firstly, the small sample size is recognized. In defence, it is argued that the samples used are highly representative (in terms of age and education), of the larger studies (e.g. Komaroff & Buchwald, 1991; Manu et al., 1993) In addition, SCL-90-R profile similarities of the CFS and depressed groups to published research tends to support the representative nature of the sample. It is also pointed out that similar sized samples have been used in the neuropsychological studies reviewed for this thesis, and have not attracted criticism for small sample size. It could also be argued that the finding of a statistically significant group difference in a small sample like the one used here might be regarded as being more significant than a similar finding in a larger group. This reasoning follows Wilson (1987) who states that in contrast to a large-group study where several individuals may be at variance with the observed effect, small-group studies require virtually all of the subjects to show the desired effect before a level of significance is reached.

A second point related to the subjects used, is the possible effect of sample homogeneity on the results. More specifically, the case matching procedure may have created a situation in which the three groups were too homogeneous (i.e. overmatched), with the resulting effect of reducing any potential group differences. Random sampling would address this difficulty, but would present additional problems in terms of the labour involved. Success in random sampling may also be limited by the multicultural composition of our South African community.

A third point concerns the failure to match the study subjects on IQ; this represents a weakness of the current study, given that intellectual level contributes to performance on several neuropsychological tests (Spreen & Strauss, 1991). While it was hoped that the educational variance, together with careful triad matching, might lessen the impact of IQ influence on test performance, this cannot be guaranteed. In defence of this omission, it is noted that age appears to be a more critical determinant of neuropsychological test performance, especially with regard to those tests that have a high loading on speed of information processing (Lezak, 1995).

The SCL-90-R was used as a measure of current psychological symptomatology at the time of assessment rather than as a basis for subject selection. Subsequent analysis of the data indicated psychological distress in some of the apparently healthy subjects, and it is possible that this may have exerted a detrimental effect on neuropsychological functioning in this group. This in turn could have reduced the significance levels of potentially discriminating test indices. Future studies might consider ensuring the "normality" of a healthy control group through more rigorous methods, such as psychiatric or questionnaire screening. On the other hand, a counterargument could be that psychological stress is a part of our daily lives, and that to try and eliminate this from healthy control groups could result in an artificially "sterile" group composition.

How suitable is the neuropsychological paradigm for the investigation of cognitive functioning in CFS and related conditions? Although some reservations about the utility of the neuropsychological measures used in this study have been expressed, it is pointed out that these tests represent the "tools of the trade", and have gained acceptance within clinical and research settings. Nevertheless, it is possible that the modest reliability of some of the measures, in conjunction with the limited normative data, may have been a threat to statistical conclusion validity. Future studies need to consider measures that have appropriate norms for the sample(s) under consideration. While the use of a control group as a comparison standard is a possible further option, the relatively small stratified sample with resultant large test score variances, obviated this possibility in the current study. In terms of the actual tests, there are indications from the current study that CFS-related neuropsychological deficits are most likely to manifest themselves on tasks that tap into supervisory or executive attentional control. Although some care was taken in selecting tests that would prove to be challenging, it may be that the challenge was insufficient in terms of level of difficulty or duration. Test developers need to address this issue by devising instruments that will place high demands on attentional functions, and be sensitive to the most subtle forms of neuropsychological dysfunction. A further suggestion with regard to the use of neuropsychological tests concerns their use with independent measures. For example, SPECT scanning and other neuroimaging techniques have been successfully used to study CFS, and could be coupled with a suitable neuropsychological battery. Although this has been attempted in a small number of studies, it would appear that further possibilities exist.

Given that neuroimaging techniques are, and are likely to remain, expensive diagnostic procedures, there is some incentive to develop a cheaper alternative in the form of a reliable neuropsychological test battery.

Finally, in terms of the psychological measures used in this study, the SCL-90-R was found to be effective in differentiating CFS from depressed patients. Independent confirmation of the discriminative ability of this instrument on similar populations is important. In addition, further investigation of the nature of the obsessive-compulsive tendencies noted in this study need to be conducted. Given the proven clinical and diagnostic utility of the SCL-90-R in other countries, some attention needs to be given to the development of a standardized version for use with South African samples.

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[1] The referencing format used here is based on the 4th edition of the *Publication Manual of the American Psychological Association* (APA, 1994). Modifications have been made with respect to the indentation of the first as opposed to second line, substitution of italics for underlining, and the omission of volume numbers (although supplement numbers have been retained). These deviations are in keeping with the recommended APA-based referencing format used by the publishers of major neuropsychological journals (e.g. Journal of the International Neuropsychological Society) and books (e.g. Lezak, 1995). It should also be noted that the referencing format for *The Lancet* changed in 1990 and so some inconsistencies will be apparent.

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APPENDIX A: INTAKE QUESTIONNAIRE

CONFIDENTIAL INFORMATION

INSTRUCTIONS: Please complete this questionnaire (its purpose is to quantify your symptom picture as far as possible). Following receipt of the completed form I will contact you to arrange an appointment.

BIOGRAPHICAL

NAME _____

ADDRESS _____

_____

TEL (W) _____ (H) _____

DATE OF BIRTH _____ AGE _____years _____ months

DOCTORS YOU HAVE CONSULTED FOR THIS ILLNESS _____

_____

CURRENT MEDICATION _____

_____

LENGTH OF ILLNESS _____years _____months _____ weeks

HIGHEST LEVEL OF EDUCATION _____

OCCUPATION _____

WHEN DID YOUR SYMPTOMS FIRST START? _____

WHEN WAS YOUR CONDITION DIAGNOSED? _____

WHAT TREATMENTS HAVE YOU UNDERGONE? _____

HAVE YOU EVER SUFFERED FROM PSYCHIATRIC ILLNESS? YES/NO _____

IF YES, PLEASE SPECIFY _____

_____

HAVE YOU EVER BEEN TREATED FOR NEUROLOGICAL ILLNESS? (EG. MIGRAINES, EPILEPSY, HEAD INJURY, ENCEPHALITIS, MENINGITIS ETC.)

YES	NO

IF YES, PLEASE SPECIFY _____

_____

HOW WOULD YOU RATE YOUR OVERALL LEVEL OF IMPROVEMENT IN TERMS OF A RETURN TO PREMORBID (NORMAL) FUNCTION? (Draw a circle to indicate position)

0--------10--------20--------30--------40--------50--------60--------70--------80--------90--------100%

0% NONE 25% MILD 50% MODERATE 75% SUBSTANTIAL COMPLETE

QUESTIONNAIRE

As it is important for us to ascertain the nature and severity of your symptoms, please complete the following:

1. FATIGUE *(Mental fatigue is the sensation of a lack of motivation and alertness. Physical fatigue is a lack of energy or strength, often experienced as muscular weakness* - note that muscle pain is dealt with in a later part of this questionaire).

HOW WOULD YOU RATE YOUR CURRENT (I.E OVER THE PAST MONTH) LEVEL OF FATIGUE? (PLEASE MARK THE APPROPRIATE BOX)

PHYSICAL

NONE	MILD	MODERATE	SEVERE

MENTAL

NONE	MILD	MODERATE	SEVERE

HAVE YOU EXPERIENCED WORSE LEVELS OF FATIGUE DURING THE COURSE OF YOUR ILLNESS?

YES	NO

IF YES, PLEASE SPECIFY_____

_____

HOW FREQUENTLY ARE YOU FATIGUED?

PHYSICAL

CONTINUOUSLY (i.e more or less every day)	SOMETIMES (a few days a week or month)	SELDOM

MENTAL

CONTINUOUSLY (i.e more or less every day)	SOMETIMES (a few days a week or month)	SELDOM

ADDITIONAL COMMENTS _____

_____

_____

IS THE FATIGUE WORSENED BY MINOR EXERTION?

PHYSICAL

YES	NO

MENTAL

YES	NO

2. DISABILITY (*This refers to a restriction of the ability to engage in the normal occupational, social and recreational activities* which results from the loss of physiological or psychological function)

HAVE YOU EXPERIENCED DISABILITY IN THE FOLLOWING AREAS?

(1) OCCUPATIONAL

YES	NO

IF YES, PLEASE SPECIFY DEGREE OF DISABILITY AS

DIMINISHED	COMPLETE LOSS

WHAT ARE THE AREAS OF YOUR JOB FUNCTION THAT YOU EXPERIENCE DISABILITY IN?_____

_____

(2) SOCIAL

YES	NO

IF YES, PLEASE SPECIFY DEGREE OF DISABILITY AS

DIMINISHED	COMPLETE LOSS

WHAT ARE THE AREAS OF YOUR SOCIAL LIFE THAT YOU EXPERIENCE DISABILITY IN?_____

_____

3) RECREATIONAL

YES	NO

IF YES, PLEASE SPECIFY DEGREE OF DISABILITY AS

DIMINISHED	COMPLETE LOSS

WHICH RECREATIONAL INTERESTS HAVE YOU BEEN FORCED TO CUT DOWN ON OR GIVE UP?

_____

_____

PLEASE COMMENT ON ANY ADDITIONAL CHANGES TO YOUR LIFESTYLE THAT YOUR ILLNESS HAS CAUSED:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

3. MOOD DISTURBANCE *(This refers to such feelings as depression, loss of interest, loss of pleasure, anxiety, sudden mood changes, and irritability)*

PLEASE INDICATE WHICH OF THE FOLLOWING CONDITIONS HAVE OCCURRED AS A RESULT OF THE ILLNESS, AND THEIR SEVERITY BY PUTTING AN 'X' IN THE APPROPRIATE BOX: (Please leave table blank if you have not experienced any mood disturbance associated with your illness)

DEPRESSION	MILD	MODERATE	SEVERE
LOSS OF PLEASURE	MILD	MODERATE	SEVERE
ANXIETY	MILD	MODERATE	SEVERE
MOOD CHANGEABILITY	MILD	MODERATE	SEVERE
IRRITABILITY	MILD	MODERATE	SEVERE

HOW OFTEN DO YOU EXPERIENCE MOOD DISTURBANCE?

CONTINUOUSLY	SOMETIMES	SELDOM

HOW LONG DO THE SYMPTOMS LAST FOR AT A TIME?

IF DAYS, STATE APPROX. NUMBER_____	IF HOURS, STATE APPROX. NUMBER_____

IS YOUR CURRENT INCIDENCE OF MOOD DISTURBANCE SIGNIFICANTLY DIFFERENT TO WHAT YOU HAVE EXPERIENCED PRIOR TO YOUR ILLNESS?

YES	NO

4. **MYALGIA** *(This refers to the symptom of pain or aching in the muscles)*

DO YOU SUFFER FROM MUSCULAR PAIN WHICH IS DUE TO YOUR ILLNESS? (N.B. NOT JOINT PAIN)

YES	NO

IF 'YES', IS THIS PAIN DISPROPORTIONATE TO THE AMOUNT OF EXERTION YOU HAD?

YES	NO

IF YOU EXPERIENCE MUSCULAR PAIN AFTER EXERTION, PLEASE INDICATE HOW LONG AFTER EXERTION THE PAIN OCCURS, AND HOW LONG IT LASTS FOR

_____

_____

WHAT KIND OF ACTIVITIES ARE LIKELY TO RESULT IN MYALGIA IN YOUR CASE?

_____

_____

PLEASE INDICATE THE SEVERITY OF THE MUSCULAR PAIN

MILD	MODERATE	SEVERE

5. SLEEP DISTURBANCE *(This refers to the change in the amount,* and quality of your sleep)

HAVE YOU EXPERIENCED SLEEP DISTURBANCE?

YES	NO

IF 'YES', IS THIS DUE TO EXTERNAL DISTURBANCE? (EG. NOISE, OR OTHER EXTERNAL FACTORS)

YES	NO

PLEASE SPECIFY

_____

_____

DID THE SLEEP DISTURBANCE OCCUR AFTER THE ONSET OF YOUR ILLNESS?

Y ES	NO

IF *NO* PLEASE GIVE DETAILS_____

_____

HAS THE DISTURBANCE OF YOUR SLEEP BEEN PERSISTENT?

YES	NO

PLEASE SPECIFY

_____

_____

PLEASE INDICATE THE TYPE OF SLEEP DISTURBANCE THAT YOU SUFFER FROM, AND THE INCREASE OR DECREASE IN THE AMOUNT OF SLEEP:

HYPERSOMNIA*	1-2 HRS	2-4 HRS	4 HRS +
INSOMNIA**	1-2 HRS	2-4 HRS	4 HRS +

**Hypersomnia refers to an abnormally increased amount of sleep.*

***Insomnia refers to reduced sleep: i.e. difficulty getting to sleep, early waking, or the feeling of having had unrefreshing sleep.*

6. OTHER SYMPTOMS OR SIGNS (*Please indicate if you suffer from other symptoms which you regard as consequences of your illness. N.B. A SIGN IS AN OBSERVABLE, PHYSIOLOGICAL CHANGE, WHEREAS A SYMPTOM CAN REFER TO ANY CHANGE IN PSYCHOLOGICAL STATE)*

PLEASE INDICATE SYMPTOM OR SIGN, AND SPECIFY ITS SEVERITY (MILD, MODERATE, SEVERE)

_____

_____

_____

_____

_____

_____

_____

_____

_____

APPENDIX B: COGNITIVE FAILURES QUESTIONNAIRE

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the last six months. Please circle the appropriate number.

	Very often	Quite often	Occasionally	Very rarely	Never
1. Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2. Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3. Do you fail to notice signposts on the road?	4	3	2	1	0
4. Do you find you confuse right and left when giving directions?	4	3	2	1	0
5. Do you bump into people?	4	3	2	1	0
6. Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7. Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8. Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9. Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10. Do you lose your temper and regret it?	4	3	2	1	0
11. Do you leave important letters unanswered for days?	4	3	2	1	0
12. Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13. Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14. Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15. Do you have trouble making up your mind?	4	3	2	1	0
16. Do you find you forget appointments?	4	3	2	1	0
17. Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19. Do you daydream when you ought to be listening to something?	4	3	2	1	0
20. Do you find you forget people's names?	4	3	2	1	0
21. Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22. Do you find you can't quite remember something although it's 'on the tip of your tongue'?	4	3	2	1	0
23. Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24. Do you drop things?	4	3	2	1	0
25. Do you find you can't think of anything to say?	4	3	2	1	0

(Reproduced from Broadbent et al., 1982, p. 15)

APPENDIX C: CFS SYMPTOM CHECKLIST

CFS SYMPTOM CHECKLIST

Please indicate with a tick any of the following symptoms that you have experienced in the past 6 months:

___ 1. Physical fatigue

___ 2. Mental fatigue

- ___ a. attentional deficits
- ___ b. calculation difficulties
- ___ c. memory disturbance
- ___ d. spatial disorientation
- ___ e. frequently saying the wrong word

___ 3. Psychological problems

- ___ a. depression
- ___ b. anxiety (including panic attacks)
- ___ c. personality changes
- ___ d. mood swings

___ 4. Nervous system problems

- ___ a. sleep disturbance
- ___ b. headaches
- ___ c. changes in visual acuity
- ___ d. numb or tingling feeling in parts of body
- ___ e. clouding of consciousness (lightheadedness)
- ___ f. frequent unusual nightmares
- ___ g. difficulty moving your tongue to speak
- ___ h. ringing in ears or alteration of hearing
- ___ i. severe muscular weakness

PTO

(Adapted from Berne, 1992, p.297-298)

___ j. blackouts

___ k. intolerance of bright lights

___ l. intolerance of alcohol

___ m. alteration of taste or smell

___ n. non-restorative sleep

___ o. decreased libido

___ p. muscle twitches

___ q. recurrent flu-like illness

___ r. painful lymph nodes

___ s. severe nasal or other allergies

___ t. weight change

___ u. muscle and joint aches with tender trigger points

___ v. abdominal pain, diarrhea, nausea, flatulence

___ w. low grade fevers or feeling hot often

___ x. night sweats

___ aa. heart palpitations

___ bb. severe premenstrual syndrome

___ cc. outbreaks of herpes simplex (fever blisters)

___ dd. uncomfortable or recurrent urination

(Adapted from Berne, 1992, p.297-298)

APPENDIX D: SUBJECT DEMOGRAPHICS

Note: Cases 1-20 (CFS group); Cases 21-40 (depressed controls)
Cases 41-60 (healthy controls)

CASE #	SEX	AGE	EDUCATION (years)	OCCUPATION
01	F	35	16	Boarded (Professional)
02	M	46	16	Boarded (Professional)
03	M	33	16	Professional
04	F	39	16	Professional
05	F	35	12	Administrative/Technical
06	F	43	12	Homemaker
07	M	52	12	Boarded (Managerial)
08	F	64	11	Retired (Professional)
09	F	22	16	Student
10	F	13	06	Scholar
11	F	45	12	Administrative
12	F	44	15	Administrative
13	F	16	09	Scholar
14	F	55	16	Boarded (Professional)
15	F	41	12	Administrative
16	F	46	11	Administrative
17	F	38	15	Professional
18	F	23	14	Student
19	M	37	12	Boarded (Commercial)
20	F	20	13	Student
21	F	34	16	Homemaker
22	M	49	17	Unemployed
23	M	32	16	Professional
24	F	39	15	Professional
25	F	35	12	Technical
26	F	45	12	Professional
27	M	51	12	Commercial
28	F	62	10	Retired
29	F	24	15	Student
30	F	13	06	Scholar

CASE #	SEX	AGE	EDUCATION (years)	OCCUPATION
31	F	47	12	Commercial
32	F	43	15	Professional
33	F	15	09	Scholar
34	F	56	17	Professional
35	F	43	12	Homemaker
36	F	46	12	Administrative
37	F	35	16	Professional
38	F	23	15	Student/articled clerk
39	M	40	11	Technical
40	F	19	13	Student
41	F	35	17	Professional
42	M	50	18	Professional
43	M	34	17	Professional
44	F	39	15	Administrative
45	F	34	12	Homemaker
46	F	43	13	Administrative
47	M	52	12	Administrative
48	F	63	12	Retired (Professional)
49	F	21	15	Student
50	F	13	06	Scholar
51	F	46	12	Administrative
52	F	48	15	Professional
53	F	16	09	Scholar
54	F	51	15	Commercial
55	F	41	12	Administrative
56	F	45	12	Administrative
57	F	37	16	Professional
58	F	23	13	Student
59	M	35	13	Commercial
60	F	21	14	Student

Note: Professional - scientists, nurses, engineers, teachers, a social worker, physiotherapist and a doctor;
Commercial - business consultant, estate agent, public relations officer;
Administrative - managers, secretaries, book-keepers, and administrative assistants;
Technical - laboratory technicians/assistants.

APPENDIX E: PSYCHOMETRIC SUMMARY SCORE SHEET

NAME: CASE #6 AGE: 43 YRS 8 MONTHS DATE: 10.09.94

PSYCHOMETRIC SUMMARY

TRAILS:	SDMT:	GROOVED PEGBOARD
A = 33	W = 59	
B = 65	O = 67	D = 55 ND = 65

PASAT:	VERBAL FLUENCY
2.4 sec = 40	F = 10
2.0 sec = 27	A = 8 Ave = 8.33
1.6 sec = 25	S = 9 TOT = 27
1.2 sec = 13	
TOT = 105	

RAVLT		RDVLT	
1 = 7		1 = 4	
2 = 10	LOT = 17	2 = 6	LOT = 15
3 = 10	STPR = 91	3 = 8	LTPR = 100
4 = 11	LTPR = 91	4 = 8	
5 = 14	Tot = 52	5 = 9	
6 = 7		Total 1-5 = 35	
Recall A = 10	Recog = 13	Recog = 13	
30 min = 10		30 min = 9	

SCL-90:		T-scores
	Somatization	69
	Obsessive/comp	72
	Interpers. sens.	64
	Depression	61
	Anxiety	67
	Hostility	63
	Phobic anxiety	65
	Paranoid ideat.	60
	Psychoticism	59
	Additional	

Profile Type

GSI = 76

PST = 67

PSDI = 77

IMPAIRED = 2
BORDERLINE = 4
LOW AVERAGE = 9
AVERAGE = 10
HIGH AVERAGE = 5
SUPERIOR = 1
% scores imp =
% scores < bord =

COMMENTS:

SYMPTOM CHECKLIST = 29

CFQ = 61

APPENDIX F: VARIABLES LIST

The following pages contain a key to the variable names which are presented in abbreviated form at the start of each SPSS/PC+™ output file.

(1) NEUROPSYCHOLOGICAL MEASURES

Variable names for the CFSDATA and TRIPLETS data files

TMTA = Part A Trail Making Test (time in secs.)

TMTAERR = number errors on Part A

TMTB = Part B Trail Making Test (time in secs.)

TMTBERR = number errors on Part B

SDMTW = Symbol Digit Modalities Test (written administration)

SDMTWER = number errors on SDMTW

SDMTO = Symbol Digit Modalities Test (oral administration)

SDMTOER = number errors on SDMTO

GPP = Grooved Pegboard preferred hand (time in secs.)

GPNP = Grooved Pegboard non-preferred hand (time in secs.)

PASAT 1 to PASAT 4 = number correct responses on the 4 trials of the Paced Auditory Serial Addition Task)

PASATOT = sum of PASAT trials 1-4

RAVT1 to RAVT5 = Auditory Verbal Learning Test (AVLT) (List A words recalled trials 1-5)

RAVTOT = total words recalled trials 1-5 (AVLT)

ERR15 = total errors trials 1-5 (AVLT)

REP15 = number of repetitions trials 1-5 (AVLT)

LEARN15 = highest number of words recalled on any trial, minus trial 1 recall (AVLT)

RAVB = recall List B (AVLT)

RAVBER = intrusions/errors on List B (AVLT)

RECALA = recall List A (AVLT)

AER = intrusions/errors on List A (AVLT)

PERCAT5 = percentage of words retained following distractor List B (AVLT)

RAVRECOG = recognition trial (AVLT)

RECOGER = recognition trial errors (AVLT)

RAV30M = 30 minute recall List A

RAV30ER = intrusions/errors on 30 minute recall (AVLT)

A LOT = learning over trials (AVLT); cumulative total of trials 1-5, minus 5 times trial 1

ALTPR = long term percent retention (based on RAV30M; expressed as a percentage of trial 5)

RVD1 to RVD5 = Visual Design Learning Test (designs recalled trials 1-5)

RVDTOT = total designs recalled trials 1-5 (VDLT)

RVDER15 = total errors trials 1-5 (VDLT)

RVDLEAR = highest number of designs recalled on any trial minus trial 1 recall (RVDLT)

RVDRECOG = recognition trial (VDLT)

RVDRECER = recognition errors (VDLT)

RVD30MIN = 30 minute recall on VDLT

RVD30ER = errors on 30 minute recall (VDLT)

VLOT = learning over trials (VDLT); cumulative total of trials 1-5, minus 5 times trial 1

VLTPR = long term percent retention of VDLT (based on RVD30MIN; expressed as a percentage of trial 5)

FASF = Controlled Oral Word Association Test (COWAT) (words generated starting with *"F"*)

FASA = COWAT (words generated beginning with *"A")*

FASS = COWAT (words generated beginning with *"S")*

FASTOT = total words generated over the 3 trials of the COWAT

FASAV = average number of words generated over 3 trials of the COWAT

SIR = summed impairment rating (based on DeLuca et al., 1995)

Variable names for the ZSCORE data file

ID = case number (1-60)

TMTA = Part A Trail Making Test

TMTB = Part B Trail Making Test (time in secs.)

SDMTW = Symbol Digit Modalities Test (written administration)

SDMTO = Symbol Digit Modalities Test (oral administration)

GPP = Grooved Pegboard preferred hand

GPNP = Grooved Pegboard non-preferred hand

PASAT 1 to PASAT 4 = trials 1 to 4 of the Paced Auditory Serial Addition Task

RAVT1 to RAVT5 = Auditory Verbal Learning Test (AVLT)

RAVB = recall List B (AVLT)

RECALL = recall List A (AVLT)

MIN30 = 30 minute recall List A

RAVTOT = total words recalled trials 1-5 (AVLT)

RECOG = recognition trial (AVLT)

RVD1 to RVD5 = Visual Design Learning Test (designs recalled trials 1-5)

RVDTOT = total designs recalled trials 1-5 (VDLT)

RVDRECOG = recognition trial (VDLT)

(2) PSYCHOLOGICAL MEASURES

Both raw scores and T-scores for the SCL-90-R are included in the variable list; there are slight differences in labelling terms between the two sets although the raw scores may be identified by the prefix RAW (e.g. RAWSOM).

Symptom Checklist - 90 - R(evised) (SCL-90-R)

SOM and RAWSOM = *Somatization* subscale (SCL-90-R)
OBSCOM and RAWOBS = *Obsessive-Compulsive* subscale (SCL-90-R)
SENSITIV and RAWSOC = *Interpersonal Sensitivity* subscale (SCL-90-R)
DEPR and RAWDEP = *Depression* subscale (SCL-90-R)
ANX and RAWANX = *Anxiety* subscale (SCL-90-R)
HOST and RAWHOS = *Hostility* subscale (SCL-90-R)
PHOB and RAWPHOB = *Phobic Anxiety* subscale (SCL-90-R)
PARAN and RAWPARAN = *Paranoid Ideation* subscale (SCL-90-R)
PSYCHOT and RAWPSY = *Psychoticism* subscale (SCL-90-R)
ADDITIT = *Additional* items (SCL-90-R)
GSI = *Global Severity Index* (SCL-90-R)
PST = *Positive Symptom Total* (SCL-90-R)
PSDI = *Positive Symptom Distress Index* (SCL-90-R)

Cognitive Failures Questionnaire (CFQ)

C1-C25 = items 1-25 of the Cognitive Failures Questionnaire
CTOTAL = summed total of the individual items of the Cognitive Failures Questionnaire

CFS Symptom Questionnaire

FATP = physical fatigue
FATM = mental fatigue
A = attentional deficits

B = calculation difficulties

C = memory disturbance

D = spatial disorientation

E = frequently saying the wrong word

AA = depression

BB = anxiety

CC = personality change

DD = mood swings

AAA = sleep disturbance

BBB = headaches

CCC = changes in visual acuity

DDD = numb or tingling feeling in parts of body

EEE clouding of consciousness

F = frequent unusual nightmares

G = difficulty moving tongue to speak

H = ringing in ears or alteration of hearing

I = severe muscular weakness

J = blackouts

K = intolerance of bright lights

L = intolerance of alcohol

M = alteration of taste or smell

N = non-restorative sleep

O = decreased libido

P = muscle twitches

Q = recurrent flu-like illness

R = painful lymph nodes

S = severe nasal or other allergy

T = weight change

U = muscle and joint aches with tender trigger points

V = abdominal pain, diarrhea, nausea, flatulence

W = low grade fevers or feeling hot often

X = night sweats

AAAA = heart palpitations

BBBB = severe premenstrual syndrome

CCCC = outbreaks of herpes simplex (fever blisters)

DDDD = uncomfortable or recurrent urination

CFSTOT = total number of items responded to in CFS symptom questionnaire

Intake Questionnaire

SEX = male/female

AGE = age in years

EDUC = education in years

OCC = occupational category

MEDIC = medication present/absent

ONSET = symptom onset preceded by flu-like illness

LENGTH = time since symptom onset (months)

SEVP = rating of physical fatigue

SEVM = rating of mental fatigue

FREQP = frequency of physical fatigue

FREQM = frequency of mental fatigue

EXERP = fatigue worsened by minor physical exertion

EXERM = fatigue worsened by minor mental exertion

OCCDYS = degree of occupational dysfunction

SOCDYS = degree of social dysfunction

RECDYS = degree of recreational dysfunction

MDD = presence of mood disturbance (depression)

MDP = presence of mood disturbance (loss of pleasure)

MDA = presence of mood disturbance (anxiety)

MDL = presence of mood disturbance (mood changeability)

MDI = presence of mood changeability (irritability)

MYALGIA = presence/absence of muscular pain

EXERT = whether myalgia is experienced after minor exertion

PAIN = severity of muscular pain

SLEEP = presence/absence of sleep disturbance

PERSIS = persistence of sleep disturbance

SLEEPTYP = type of sleep disturbance (insomnia/hypersomnia)

IMPROV = subjective rating of percentage return to premorbid functioning

VIRAL = presence/absence of viral antigens (as confirmed on laboratory testing)