# NEUROPSYCHOLOGICAL AND PSYCHOSOCIAL ASPECTS OF CHRONIC FATIGUE SYNDROME

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## Dedication

To Terry without whom this would not have been finished. To Stephen and Peter who missed their summer holiday and Mummy some of the time and to Sue who enabled me to do this research.

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## ABSTRACT

This Thesis reports a full scale study of cognition and mood in Chronic Fatigue Syndrome (CFS) longitudinally during recovery. Previous studies fail to cover the scope of this study and/or fail to define adequately the syndrome for subject selection.

47 CFS patients were compared with 41 normal and 26 Crohns/colitis controls in a longitudinal study of cognitive performance and depression/anxiety scores.

CFS patients performed significantly worse than controls on many of the cognitive tests at first testing. Small but significant differences between CFS and normal controls were found on memory tests (Logical Memory, Word Recognition and, more significantly, Rey Complex Figure) but Crohns/colitis patients scored similarly to CFS, suggesting that this might relate to a general problem such as attention. Much larger and more significant differences between CFS and both control groups were found on tests involving a psychomotor component (e.g. Reaction Time, Finger Tapping and Digit Symbol). CFS patients' performance improved over time (above practise) on word recognition, Stroop (colours), Reaction Time (Movement) and Digit Symbol.

CFS patients were significantly more depressed/anxious than the control groups and scored higher on Middlesex Health Questionnaire (Psychiatric). Depression/anxiety did not diminish significantly by second testing. Differences on depression scores accounted for some of the differences in cognitive test performance, in particular Word Fluency and Stroop; however, significant differences remained after ANCOVA removed depression: significant differences remained on Logical Memory, Word Recognition, Digit Symbol, Finger Tapping and Reaction Time.

It was concluded that CFS patients were slowed on psychomotor tasks and that this was only partly accountable by depression as suggested by depressed score. CFS patients performed slightly worse on some other tests possibly dependant upon the task demand. Digit Symbol, Reaction Time, and Finger Tapping seemed to be most sensitive to CFS. Brain damage was not necessarily indicated by the results: differences in psychomotor performance could be caused by difficulties in the transmission of instructions to the muscle or slowness in the nerves and muscles themselves. CFS patients' performance significantly improved on a number of tests over time, and did not significantly deteriorate on any test; therefore, the trend of CFS patients' test performance overall was to get better not worse over time.

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# CHAPTER 1. INTRODUCTION

This thesis examines patients' cognitive performance during recovery from Chronic Fatigue Syndrome (CFS).

In the literature up to 1989 little had been done to establish why CFS patients complained of problems with cognition, particularly memory. Later literature did not look at cognition in terms of change during the illness. This research firstly attempts to establish the extent and nature of CFS patients' cognitive problems and secondly how performance changes during recovery.

The literature shows that CFS patients are more depressed and anxious than normal controls. This has not previously been assessed in relation to performance on cognitive tests. This thesis examines thirdly the extent to which mood variables in CFS patients could account for poorer performance on cognitive and psychomotor tests.

The design of the study is longitudinal with three groups: CFS, normal controls and Crohns/colitis controls. CFS patients were from Ruchill Hospital (Glasgow) Outpatients'department, normal controls were from St Andrews' Ambulance evening classes and Crohns/colitis patients were from Stobhill Hospital (Glasgow) Gastroenterology outpatients' clinic.

Patients were seen up to three times with a minimum of 4 months in between. They were tested on a standard set of cognitive and psychological tests and some tests of attention and speed developed at Stirling University. The memory tests were varied as necessary at each testing. The drop out rate for patients was high and not all patients completed the test set. The data were analysed using SPSS-PC.

# CHAPTER 2. LITERATURE SURVEY

## 1. What is CFS ?

Chronic Fatigue Syndrome (CFS) is a syndrome, recognised by a pattern of symptoms. CFS was first recognised in the medical domain but has subsequently been thought to involve psychological factors.

### 1.1 Estimated prevalence of ME/CFS

CFS is a term recently given to a syndrome the main symptoms of which are chronic fatigue and muscle fatiguability. It is a new term largely replacing that of Myalgic Encephalomyelitis (ME), with which it is associated, but it may not be synonymous. The number of patients suffering from CFS or ME in 1988 was put at 150,000 sufferers in the UK, 10,000 in Australia, 3,000 in New Zealand and 3,000 - 5,000 in South Africa according to Spracklen (1988). Numbers in America may be much higher: Gorensek (1991) estimates that new cases of CFS approximate 6000 per annum. The effect in terms of lost earnings in the UK is placed at £300 million annually by Ramsay and Dowsett (1992).

### 1.2 Naming of CFS

Myriad names have been given to, or thought to be the same as, CFS. The main ones are discussed below. Hyde (1992(a)) has produced a compendium of associated names, which is reproduced in Appendix 1 Table 2. The problem of defining and naming this syndrome is discussed here with reference to its history. The use of the new term CFS which is defined by symptom-based criteria is in itself an attempt to move the illness away from its historic links and its presupposed organic components. Early terms include names referring to the first outbreaks: 'Royal Free Disease' and 'Iceland/Akureyi Disease'. The term Myalgic Encephalomyelitis (ME) is a medical description based on

the early assumptions about the illness, myalgia meaning muscle pain, encephalitis inflammation of the brain, myelitis meaning inflammation - usually of the spinal cord. Hence the literal meaning is muscle pain with inflammation of the brain and spinal cord.

The literal meaning of ME is not a description which fits the majority of today's patients. The term benign was often attached to names to indicate the non-progressive nature of the disease. Wookey (1978(b)) objected to the term benign being used on the grounds that the syndrome can have serious after effects. Coupled with the term benign, the name neuromyasthenia, literally meaning neurological muscle debility, was widely used. Compston (1978(b)) describes myasthenia as muscle weakness or fatigue, its literal meaning, but Behan (1978) objected to neuromyasthenia on the grounds that it unjustifiably implied a lesion in the neuromuscular junction.

In America the name Post Infectious Neuromyasthenia (PIN) became popular; it suggested a post-illness syndrome. In Britain the name Post Viral Fatigue Syndrome, widely used in the late 70's and early 80's, also indicated a post illness syndrome. The hunt for a trigger illness began but what soon became evident was that no one illness could be said to be the cause. In America it was called Chronic Epstein Barr Syndrome as a reflection of the association with EBV virus. In most places it was first associated with polio and then Epstein Barr Virus but in Scotland in the 80's it became attached to another virus, Coxsackie B virus. Today the Americans call the syndrome Chronic Fatigue Syndrome, and Chronic Fatigue and Immunodeficiency Syndrome (CFS and CFIDS), indicating either a neutral or immune basis. In Britain the term CFS is used but not CFIDS. In this thesis the term used is that of the paper discussed, or ME to describe the early epidemics and CFS to describe the syndrome in general.

## 1.3 The pattern of symptoms

Descriptions of CFS and ME vary, but Table 1 shows the main symptoms as observed by various doctors and researchers from 1955 - December 1992. Apart from fatigue and

**Table 1 Symptoms as described in date order**

| | Macrae & Galpine 1954 | Ramsay 1978 | Hill et al 1959 | Dillon 1978 | Corridan 1978 | May et al 1980 | Bishop 1980 | Keighley & Bell 1983 | Hamblim et al 1983 | Calder & Warnock 1984 | Behan et al 1985 | Durndell 1988 | Altay 1990 | Stricklin 1990 | Petersen 1991 | Wong et al 1992 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Like polio | R.F. 1955 | E.M.E. | E.N. 1970 | E.N. | Benign M.E. | E.M.E. | Sporadic M.E. | I.M. | Coxsackie B | ME | ME | P.I.N. | E.N. | CFS | CFS |
| Fatigue | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Muscle pain | X | X | X | | X | X | X | | X | X | X | X | X | X | X | X |
| Muscle weakness/ fatiguability | X | X | X | X | X | X | | X | | X | X | X | X | X | X | X |
| Headache | X | X | X | X | X | X | | | X | X | | X | X | X | X | |
| Dizziness | X | X | | X | | X | X | X | | X | X | X | X | X | | |
| Sore throat | X | X | X | X | | X | X | | X | X | X | X | X | | X | |
| Lymphadenopathy | X | X | X | X | X | | X | | X | X | | | X | X | X | X |
| Depression/anxiety | X | | X | X | | | | | | | X | X | X | X | X | |
| Tinnitus/deafness (*) | | | X | | | | X | X | | | X | | | X | | |
| Nausea/vomitting | | X | | | | X | | X | | | | X | | X | | |
| Temperature | X | | X | | X | | X | | | | X | | X | X | X | X |
| Diplopia/photophobia | | | X | X | X | | X | X | X | | | X | | X | X | |
| Diarrhoea/constipation | | | X | X | | | X | | X | | X | X | | X | | |
| Paraesthesia | | X | X | | | X | X | | | | | | | X | | |
| Concentration/memory | | | X | X | | | | | | X | X | X | X | X | X | X |
| Sleep disturbance | | X | X | | | | | | X | | | X | | X | X | X |
| Tachycardia/palpitations | | | | | | X | | X | X | X | | | | X | | |
| Joint pain/stiffness | | X | X | | | X | X | | | X | | X | | X | X | |
| Personality changes | | | X | X | | X | X | | | | | | | X | | |

Note:

E.M.E Epidemic Myalgic Encephalomyelitis
R.F. Royal Free disease
E.N. Epidemic Neuromyesthenia
I.M. Infectious Mononucleosis
P.I.N. Post Infectious Neuromyesthenia

Other symptoms include:
confusion, stiff neck, respiratory problems, colour changes, lower limb clonus, finger-to-nose touching problem, injection of conjunctival blood vessels, abdominal pain, dreams, anorexia, bladder problems, earache.

(*) includes sensitivity to noise

muscle fatiguability, symptoms included lymphadenopathy and fever, prolonged painful muscle spasm, bladder dysfunction, paraesthesia, neck rigidity, tenderness in ribs, liver edge palpability, headache, vertigo, pain in limbs, sore throat, impairment of sensation, allergies, weakness and fatigue (Compston 1978(a), Ramsay 1981).

The two key symptoms described in the earliest reports of ME and the latest reports of CFS are fatigue and muscle weakness. These symptoms among others are considered in the following sections.

### 1.3.1. Fatigue

Fatigue symptoms are very common in everyday life. Grafman et al. (1991) say that the seventh most common presenting symptom in the USA is fatigue. They quotes Kennedy (1988) as estimating that half of these cases are due to psychiatric problems.

Wessely has made an important contribution by looking at the type of fatigue in CFS. Wessely (Wessely and Powell 1989) shows fatigue in PVFS patients to be more like that in depressed patients than in those patients suffering from neuromuscular disorders. Wessely (1990(b)) reports finding psychiatric indicators which could be causing fatigue symptoms in over 70% of 47 consecutive fatigue patients.

Wessely (1989) considers both fatigue and viral infection to be very common and occurring more in women. Wessely (1989) quotes 20% (30% in women) of the adult population (Britain) as complaining of fatigue. He reports that in the 35-54 age group, 30% report having had a virus infection in the last month; there is, therefore, a large overlapping population, who suffer fatigue following a virus.

Strong associations with fatigue are physical activity (a lot of athletes complain of CFS: Shaw 1987; Holoway 1993), depression, anxiety and emotional stress. Therefore Wessely (1989) considered CFS to be a label for the common occurrence of fatigue

which is commonly caused by these factors.

The argument that CFS is just a label for common fatigue is not borne out by looking at the distribution of fatigue in the population. In a paper of which Wessely is co-author (Lewis and Wessely 1992) the authors point out that the distribution of fatigue in the general population shows the opposite direction of gradient to that of CFS patients: i.e. fatigue is higher in working class populations but CFS is commoner in middle class populations. He attributes this to health utilisation differences (i.e. middle classes use the health service and get a CFS diagnosis) but nevertheless it somewhat weakens his case that CFS may just be the extreme end of the common complaint of fatigue.

The problem is that fatigue is hard to define and even harder to measure (Barofsky and Legro 1991). Since measurement of fatigue is linked to activity, motivational or psychological explanations are often considered. The following papers suggest other explanations for fatigue. Wood et al. (1992) found diurnal variation in energy in patients with CFS, with peaks at 10.00-12.00 a.m.; this is similar to controls but the average at any one point in time is lower for CFS patients, and recovered CFS patients fall between the two groups. They find energy levels, both mental and physical (they are highly correlated to each other), to be highly correlated with positive affect but to be not significantly correlated with negative affect. This suggests that positive enhancement of mood does decrease fatigue in CFS patients but that, contrary to what might be expected, negative mood is not causing fatigue. Moldofsky's (1989) review suggests that CFS patients have abnormal alpha EEG (non REM sleep) tests; this might indicate non-restorative sleep leading to extreme fatigue. Stephenson (1989) saw children with Coxsackie B and fatigue. Their families were social class 1 and 2. He used a modified Romberg to test the patients and suggests that the results show a central brain origin of fatigue. Wong et al. (1992) tested muscle and performance in CFS and concluded that CFS patients reach exhaustion much more rapidly than normals due to a metabolic defect. They suggest that the CFS patients experience of overwhelming tiredness at rest might have a similar etiology.

Fatigue in CFS patients is a difficult symptom to assess. There is little evidence for any organic cause to fatigue in CFS patients and a strong argument for psychological etiology. Extensive tests in 100 severely fatigued patients, by Lane et al. (1990), found scant physiological evidence of abnormality except for a few cases of thyroid abnormality.

### 1.3.2 Medical abnormality and symptoms in CFS

In the early ME literature, four pieces of objective evidence suggested an organic basis to CFS. Firstly, Jelinek (1956) discovered that it appeared possible to transmit CFS via blood from humans to monkeys. Secondly, Cerebral Spinal Fluid (CSF) was found to be abnormal in patients identified in particular outbreaks of ME ("A New Clinical Entity" 1956; see Appendix 1 Table 6). Thirdly, Electroencephalograph (EEG) scans on 40 CFS patients showed 75% had an excess of irregular, intermediate slow activity similar to that found in glandular fever or MS patients (Pampiglione et al. 1978). Fourthly in Akureyi the spread of a later polio epidemic failed to occur in the area where the Akureyi (ME) epidemic had taken place and children from the Akureyi area when vaccinated against polio showed greater antibody increase than other children. (Hyde 1988, Hyde and Bergman 1991, Sigurdsson 1958 in Hyde 1991). More recent evidence suggests pituitary-hypothalamic dysfunction in a group of CFS patients, and single photon emission computed tomography (SPECT) scans on CFS patients suggest possible decreased blood flow in parts of the brain (see Neuropsychology part 3.5).

Redmond (1991) writes that the way abnormal tests in CFS patients are reported leaves much to be desired, and a more scientific, statistical analysis of such results is needed. The evidence for organic causes of symptoms has been fragmentary, as described in the following paragraphs. When discussing the CFS symptoms below, account is taken of the possibility of organic abnormality being their cause.

### 1.3.3 Muscle Weakness

Muscle fatiguability, tired and aching muscles are the second most important problem in CFS. By muscle fatiguability we mean the loss of performance of the muscle (as perceived by the patient) not just the general feeling of tiredness all over. Other illnesses show similar combinations: the combination of muscle weakness and fatigue is found in hypothyroidism and hyperthyroidism and as is indicated by Demitrack et al. (1991), mild thyroid problems are found in larger than normal proportions in CFS patients. In these thyroid conditions weakness can be accompanied by wasting although muscle enzymes are normal; thus the weakness experienced by CFS patients may be real even if muscle tests are inconclusive.

Differences in muscle tissue are also found in healthy people. Simply not using the muscles will cause deterioration, so that if a patient goes to bed for a long period he/she is likely to experience loss of muscle tone and tired and aching muscles. Athletes show differences according to the type of activity, for example where athletes require speed as opposed to stamina more type II than type I muscles are found. Therefore not only might one have muscle problems without corresponding evidence but abnormalities which we do find may in fact be no different than that found in some groups of normal people.

The muscles undergo chemical and other changes during exercise, and in CFS patients problems occur most on exercise. In polio the muscles attacked are those normally most used, and polio is an echo virus with associations with ME. In terms of activity, abnormalities are found in CFS patients on exercise. R.P. Taylor (1989) reports a muscle abnormality in the rotation of energy; by this he means abnormality in the chemical changes that take place in muscle during exercise; he estimates a 20% decrease in energy, and an increase in energy store utilisation. Arnold et al. (1984) reports a case study showing increased acidosis in the muscle during aerobic work. Wong et al. (1992) reports that duration of exercise in 22 CFS patients is markedly

shorter, changes in phosphocreatine, inorganic phosphate and pH occur more quickly in CFS patients and they have less adensonine triphosphate at exhaustion. Wong et al. conclude that CFS patients have a defect of oxidative metabolism with a resultant acceleration of glycolysis in the working skeletal muscle. McClusky (1990) shows an overproduction of lactic acid during activity in CFS patients. Behan et al. (1985) report that muscle biopsies were done on CFS patients, showing muscle to be abnormal and patients to have muscle weakness up to 3 hours after continuous exercise of 1 hour.

Not everybody has found the muscle performance to be poorer in CFS patients; Stokes et al. (1988) tested muscle strength in 30 patients, they found that patients were neither weaker nor more fatiguable than controls. Coakley (1989) refutes the statement in Shepherd (1989) argues that change in muscle protein synthesis occurs in CFS and suggests changes are due to inactivity in CFS patients and that gradual increase of exercise tolerance should be encouraged for CFS patients.

On testing of the muscle tissue, other abnormalities have been found. Byrne et al. (1985) find a moderate increase in Type II fibre in muscle. Doyle (1990) finds this Type II predominance and abnormalities in nerve ending and muscle meeting places. Doyle does not think these could be accounted for by disuse. Jamal finds abnormal jitter in muscle (Jamal and Hansen, 1985) in ME patients; in a recent debate on his work (Jamal 1990) he suggests that this is due to a defect in the way nerve impulses are transmitted along the muscle fibres. The presence of Coxsackie B virus has been found in muscle tissue (Behan 1985; Archer 1987) and ribonucleic acid (RNA) from entero viruses has been found in 24% of ME patients' muscle biopsies (Gow et al. 1991).

Lewis and Haller (1991) advocate that exhaustion from whole body exercise is most important in CFS and treadmill or similar exercise in CFS should be tested. They discuss other disorders and say that increase in arteriovenous oxygen difference accompanied by normal maximal cardiac output is suggestive of an impairment in the utilization of oxygen by muscle 'but that present biopsy data on a muscle oxidization

abnormality is inconsistent'. Wong et al. (1992) however show cardiac abnormality does not seem to be the problem in CFS, rather the problem is of metabolic changes, as found in earlier studies.

In CFS patients various muscle abnormalities have been found but the importance of these and the extent to which they are part of a disease process is debatable. Further evidence from studies using more patients and control data needs to be obtained. The problem is that, so far, a high incidence of an abnormality has not been found across many groups. There is also uncertainty as to the meaning of such results as are available.

In conclusion, from the evidence that is available, it seems probable that:

1) CFS patients fatigue more quickly than normal with prolonged or repeated exercise;
2) the muscle of CFS patients may contain enteroviruses;
3) the muscle of CFS patients has more Type II fibres than normal;
4) the muscle of CFS patients during exercise fails to uptake enough oxygen and chemical changes occur more quickly.

1), 3) and 4) may possibly be accounted for, in part, by differing patterns of exercise and 2) is not shown in all patients.

### 1.3.4. Viral infection and implications in CFS

Viral illness, as stated earlier, is extremely common and a particular virus may have more effect on some people than on others.

It is important to note that certain features of epidemics of ME have similarities to viral epidemics. This is perhaps easiest to see in the early outbreaks, for example at the Royal Free, where lymphadenopathy, fever and length of transmission seem consistent. The same type of symptoms are still seen in CFS. Temperature changes and swollen glands, normally regarded as signs of infection, are common in the early stages, hence

the "post viral" and "yuppie flu" labels. The more severe symptoms of ME - paraesthesia, photophobia, psychotic symptoms, and symptoms associated with encephalitis - have been observed in echo viruses, e.g. polio, Coxsackie B and herpes virus. Neurological symptoms (including photophobia, confusion and loss of concentration) in CFS are similar to those caused by some viruses. Symptoms that are usually regarded as psychiatric, e.g. depression, sleep problems and anxiety, are often seen in prolonged or severe bouts of viral illness and the echo viruses that have been implicated in ME and CFS have been known to produce psychiatric symptoms (Abbey and Garfinkel, 1991).

CFS could be caused by a new virus: over the last decade the number of neurotropic viruses and bacteria has increased. This includes an increasing range of familiar pathogens as well as new pathogens (Kennedy 1990).

The first waves of CFS (as it has become known) were seen in association with polio. The 1981 wave in Scotland in association with Coxsackie B and in America and the South of England in connection with Epstein Barr virus (EBV). In the case of EBV and Coxsackie B the presence of these viruses has been definitely identified in high levels in CFS patients (Strauss et al.1985; Keighley and Bell 1983). In the Lake Tao outbreak however, raised antibodies were found to many viruses not just EBV (Buchwald et al. 1992). Mowbray (1992) reports that 25% of CFS patients had active enteroviruses. Jenkins (1991) suggests that CFS illness may occur largely in temperate climates being spread at similar times to that when echo viruses are known to be most active. Evidence of numerous viruses were found in the early epidemics, not just those with which CFS has been associated. Acheson reports the large number of viruses found in tests in early epidemics: see Appendix 1 Table 8 (Acheson 1959). However no one particular virus has been consistently found and although viruses are harder to isolate than bacteria, the evidence does not favour a single viral cause.

Other explanations of how viruses might be part of a combined causal etiology follow a number of themes:

1) Poor response to viral infection

Miller (1991) discusses the need to assess the role of a virus in a patient's illness more thoroughly, rather than just taking one viral measure. He suggests studying viral burden, strains of virus, sites of viral replication, and state of virus. Factors such as the inability of patients to make antibodies to a component of Epstein Barr Virus Nuclear Antigen (EBNA-1) and functioning of T cells may be more important than the level of virus in the blood. This type of approach on large groups of patients might give us a better overall picture of viral involvement.

2) Poor psychological response to viral illness

Byrne (1988) states that "a reasonable view of the RF epidemic is that an infective agent, probably viral, led to an illness ... against this background some patients develop hysterical neurological signs probably due to hyperventilation".

3) Viral damage

Weir (1989) proposes that viral infection leads to an incomplete immune response, causing chronic infection, which results in inflammation and thus clinical features. EBV affects deoxyribonucleic acid (DNA) and can profoundly affect T cell suppression. It is not enough to look at short term effects in the patient; this virus and others may be profoundly modifying immuno-response in later years.

4) Persistent viral infection

Southern and Oldstone (1986) show how viruses manage to evade the immune system and remain in the body. They may mutate frequently thus avoiding annihilation by antibodies. The resulting illness may not be directly caused by the virus but the illness may result from the body's successive attempts to produce antibodies causing an overload in the immune system. Thus the changing properties of viruses, rather than

a particular virus may cause CFS.

Mims (1978) argues that persistent viruses are not new but that there have been, for a long time, viruses that are well adapted parasites able to elude the immune system and maintain themselves. He states "Most persistent viruses infect lymphoreticular tissues" and this is interpreted by suggesting that it results in an impaired immune response to the infecting virus which in turn favours persistence. Mims goes on to say that the biological function of transformation and the integration of viral into host DNA means that the infection is able to persist in the host and undergo reactivation. This sort of evidence has been found in CFS patients; Hughson (1988) finds enterovirus infection persisting in muscle tissue. Archer (1987) reports evidence of excessive muscle fatigue due to persistent viral infection in CFS patients.

Therefore, it is possible that viruses are persisting longer in the body than previously and causing longer, variable but persisting illness. Most of the viruses mentioned so far in connection with CFS and ME are echo viruses; it is suggested that a virus of that family similar in constitution and residing in the gut may be the cause of CFS. It could be parasitic in some way linked to the virus. It is possible that CFS is caused by any echo/enterovirus. The early epidemics of ME tended to occur in temperate regions between May and October: this is the time when echo viruses would be most active (Jenkins 1991).

5) Viruses in combination

Some theories as to the role of viruses in CFS involve a combination of viruses, for example: Coulter (1988) suggests that CFS may be caused by virus combination, possibly cytomegomegalovirus or HHV6 (human herpes virus 6, previously called HBLV) in combination with EBV. Dubois et al. (1984) describe myalgia and fatigue symptoms as in CFS with reference to persisting EBV and Cytomegalovirus.

Others attribute CFS to viruses in general; Bishop (1980) describes the syndrome in current cases; he considers it most likely to be an antecedent of viral illness.

### 1.3.5 Immune competence in CFS patients

The immune competence of a patient is of vital importance in the patient's ability to cope with illness. The importance of viral illness in the development of CFS may be in its effect on the immune system.

EBV virus, with which CFS/ME has long been associated, is well known to cause longer term immune problems in some patients. In rare cases, infectious mononucleosis may cause a fatal lymphoproliferative disease. DuBois et al. (1984) state that infectious mononucleosis develops in approximately 50% of adults and life-long viral latency is established. In his study 71% (n=10) have mild deficiency of one or more immunoglobulin isotypes and minor T cell abnormalities are seen in 6 out of 7 patients studied. Hamblain et al. (1983) examined patients with infectious mononucleosis and who went on to develop chronic ill health. They find an increased number of T suppressor cells and fewer T helper cells in patients after infectious mononucleosis. Evans (1991) discusses the relationship of immune changes to EBV virus. He says that some patients with EBV virus have lack of antibody to all or part of EBNA; however, similar EBV and immunocompetence findings are seen in people with high stress by Kiecolt, et al. (1984), who discuss first year medical students before and after an exam and care-givers to Alzheimer sufferers.

The problem is that most people come into contact with EBV without long term complications, so that presence of EBV does not help us to distinguish CFS patients from the normal population. Holmes et al. (1988) discuss the role of EBV in CFS, and suggests that EBV is not an adequate explanation for CFS. Fifteen symptomatic cases are reported and compared to non-case serologically positive controls; they suggest an immunological origin. However, neither serological positive tests nor EBV titres

necessarily distinguish case and non case.

When looking at CFS patients, many abnormal immune complexes have been recorded. For example: DuBois (1984) reports that sereological tests on CFS patients show abnormal immunology due to previous major illnesses. The following deficiencies in CFS have also been reported: Read et al. (1988) report IgG1 Subclass deficiency and Staines (1985) adenylate deaminase deficiency syndrome. Simpson (1990;1986) finds that ME subjects have the lowest percentage of normal red cells and the highest incidence of cup forms compared to blood from Multiple Sclerosis patients and healthy controls. Prieto et al. (1989) find that increased opioid activity, through a classical receptor mechanism, is active on a higher proportion of ME patients than controls. Mayne (1970) reports transient gross abnormalities in red cell morphology from ME patients from Adelaide; he suggests, therefore, that abnormality in oxygen delivery is the cause of ME.

These kind of studies on CFS patients show, however, the characteristic findings of minor abnormalities or unusual test results that are found with a CFS patient population. These results have not been consistently found or found in large samples; thus the importance of them is still very debatable. The most common finding (Thomas and Dillon 1978) is of positive monospot tests indicating a high white blood cell count, suggestive of allergy or infection or possibly immune overactivity.

Some researchers into CFS have pointed out the similarity with effects of high Interferon levels in the blood in patients (Strauss et al. 1988(a); Lloyd et al. 1988; Lever et al. 1988). Smith (1989) suggests that slowed reaction time in CFS patients is similar to patients with high Interferon levels due to a cold.

The use of immunoglobulin as a treatment for CFS to counteract immune problems has not met with great enthusiasm. Although Lloyd et al. (1990(b)) find significant improvement above placebo with immunoglobulin, Petersen (1990) does not, and the

procedure is costly and intrusive. The use of Acyclovir, an anti viral agent used in herpes type 6 virus, has also been used to treat CFS without much success (Strauss et al. 1988(b)). Thus viral involvement in CFS appears to involve a complex relationship with the illness, and treatments directed at a virus or immune abnormality have not worked as a cure for CFS.

### 1.3.6 Symptoms compared to normal population

CFS patients present as a distinct group because their individual histories of illness are similar and because they report a similar group of symptoms, with fatigue and muscle problems the highest. Durndell (1988) shows that their symptom-reporting cluster is distinct. Durndell examines the symptoms of ME patients (as diagnosed by General Practitioners (G.P.'s) or consultants) compared to normal controls. What he finds is not common symptoms exaggerated by the ME group but a different pattern of symptoms with high agreement within the ME group. The report about the cluster of ME patients at Glasgow's College of Technology records the incidence of symptoms for ME and controls. ME patients complained of the following symptoms in the percentages given: fatigue 91%, weakness 95%, loss of concentration 91%, sore eyes 86%, looking pale or grey 86%, heavy legs 82%, feeling hot or cold 82%, depression 82%, loss of memory 77% and sensitivity to light 73% as the most common of their symptoms. Normal controls reported all these symptoms at a much lower level (12%,12%,31%,27%,23%, 8%,19%,12%,3%,19% respectively). Normals reported different symptoms as most common; the top being headache 62%, sore throat 46%, cold in the head 42%, muscle pain in back, arms or legs and these are reported at a similar level in CFS patients. This suggests that CFS patients are not just overstating, nor are they at the extreme end of the symptom range of normal healthy people, but rather that they are giving a different set of symptoms, plus some ordinary symptoms common to the general population at the normal rate.

Durndell's analysis suggests symptoms such as headache or sore throat may not be the most distinctive symptoms of CFS. His study suggests that there are more unusual symptoms that seem indicative of CFS but are rare in the normal population. These symptoms include loss of memory/concentration, sore eyes, looking pale, feeling hot/cold and sensitivity to light. These symptoms fall into two categories: 1. a problem with autonomic regulation e.g. temperature and 2. neurological type symptoms.

One problem with Durndell's (1988) study is that cases are defined by diagnoses from a wide group of people i.e. different consultants and G.P.'s. However, the population from which he selects is limited to the Glasgow Polytechnic over a specific time period; this is similar to the way early ME epidemics were defined (type 1 definition: see following section 1.4.3).

### 1.3.7 Summary of 1.3

The main symptoms of CFS are common in the normal population; they are not symptoms which are distinctive taken individually. The symptom combination and weighting of some symptoms is distinctive, according to the work of Durndell (1988,1989). The medical evidence for abnormality in CFS is fragmentary; most reports of such abnormalities are of small groups.

## 1.4 Diagnosis and Definition

### 1.4.1. The need for clear defining of CFS

The early accounts of ME describe its symptoms. This, in itself, is not adequate to allow comparisons between individual patients or groups of patients. In order to be able to compare information and research, the basis on which diagnosis of CFS takes place must be known. Ideally, the same criteria would be used for all research on CFS; today this is still a long way off. However, papers from the 1980's onwards have at least begun to state the grounds on which patients have been diagnosed as CFS.

One of the reasons definition has been more complicated in CFS is that it has been dealt with by different medical specialist departments. Sharpe et al. (1991) make the observation about CFS that: 'research (is) carried out by investigators in different disciplines using different criteria to define the condition'.

The situation today is described by Holmes who sums up the problem of definition as follows: 'many investigators have continued to use their own diagnostic and screening criteria for CFS-like illnesses but fail to adequately describe their methods, negating the scientific value and comparability of their results with other reports.' (Holmes 1991).

### 1.4.2 The way in which CFS has been defined

CFS has been defined largely by its symptoms. Section 1.3 points out that the evidence of organic abnormality in CFS is largely fragmentary and insubstantial. For a long time CFS type illnesses were not evaluated against any definite criteria. Modern definitions of CFS vary substantially and depend on clinical judgement of symptoms.

Why now do we have definitions largely based on subjective assessment of symptoms? CFS / ME cannot be shown to be related to (only) one virus, it does not affect (only) one area or process in the body, it cannot be distinguished by one specific physical test and its symptomatology has varied over time. Acheson (1959) indicates a number of important points about defining the syndrome: (a) no deaths have occurred, (b) no causative or toxic agent has been discovered, (c) recognition must be on the clinical and epidemiological pattern. Since definition according to epidemiology has problems due to the change from epidemic to sporadic occurrence, the clinical picture - i.e. symptoms - has become the main criterion.

### 1.4.3 Type of definition of CFS in the literature

The ways CFS has been identified or defined in the literature can be classified into four methods:

1) The syndrome is defined by describing a group of patients' symptoms, e.g. Pampiglione et al. (1978).
2) The patient group is defined by being diagnosed as CFS or PVFS or ME by a particular group of doctors e.g. Durndell (1988), Stricklin et al. (1990).
3) Criteria used are from published papers such as Holmes (1988) e.g. Hickie et al. (1990); Lane et al. (1991); Hayden (1991); and Mckenzie criteria in Blakeley et al. (1991); Dawson (1990) criteria are given in Lynch et al. (1991).
4) Researchers' own criteria are given for the definition of the group, often based on method 3 above e.g. Whelton et al. (1992).

The use of definition method 1) involves no strict applied criteria and therefore definition is poor, although its use is becoming less common. The problem with definition 2) above is that we are not privy at all to what criteria has been used. Katon et al. (1991) say that Holmes' criteria are not used and that patients are referred from G.P.'s or self-referred. It is inadequate scientifically not to know which criteria are being used. 3) and 4) are the most satisfactory methods but Holmes' criteria has been subject to much criticism.

### 1.4.4 Mis-inclusions and exclusions

The differences in diagnosis of CFS/ME/PVFS has created the problem of people who are diagnosed CFS who should not be (i.e. false positive) or not diagnosed CFS who should be (false negative or not selected as a possible diagnosis). Note that these refer to exclusions and inclusions in criteria for the diagnosis of CFS, not exclusions for methodological reasons in research.

Definition 1) in the previous paragraph would tend to include false positive mistakes since the syndrome was described from all the similar patients that were seen, rather than the

patients symptoms being checked against those known in CFS/ME. There is evidence of this kind of mistake where patients diagnosed as ME were found to have Multiple Sclerosis (MS) at post-Mortem ("Epidemic Myalgic encephalomelitis" 1978). The signs and symptoms of MS are given in Appendix 1 Table 12 from Poser (1992). The early symptoms of MS overlap considerably with those of ME patients (muscle weakness, visual problems, paraesthesia, dysarthria) but it would be rare to see the signs Poser mentions. The inclusion of a MS patient under the diagnosis of CFS/ME is less likely today with clearer diagnostic guidance. The inclusion of patients who are suffering from primary psychiatric disorder; particularly Major Depressive Disorder (MDD) is a more major diagnostic issue as discussed in Section 1.4. (These psychiatric patients may be included in some studies and not in others and fundamentally change the results for any one group of patients.)

Mis-inclusion is a problem, but in defining CFS the exclusion of patients is as great a problem. When definition of CFS is by symptomology, and then exclusion is by certain criteria, as in 3) and 4), it can seem to be rather arbitrarily drawing a line between patients who are to be included and those who are to be excluded when in fact there is little difference between them. Price et al. (1992) in their study of the prevalence of CFS in the community show this quite clearly. Ninety percent of those diagnosed by positive criteria (fatigue and disability) for CFS were excluded by negative criteria in the Price population study. The exclusion criteria for Price's study include prior psychiatric history, medical diagnosis of a different substantive medical condition, substance abuse or weight loss.

The exclusion criteria for defining CFS in Price's study have become more important than positive criteria. The over-importance of exclusion criteria causes two main problems:

1) people may be included whose medical condition is not different from that of excluded patients, who will later be diagnosed as having recognised physical or mental disorder.
2) People may also be excluded who are experiencing CFS in addition to the problems

for which they are excluded.

Apart from the mis-inclusion of Multiple Sclerosis, which is perhaps less likely today, there are a number of conditions which may considerably overlap with CFS. These are discussed in Section 1.5. Other illnesses share similar early signs but can be distinguished easily if the right test is done e.g. hypothyroid and other thyroid conditions.

### 1.4.5 Established criteria and differences in inclusions and exclusions

The need to classify individual cases and compare outbreaks and the demand for research meant that researchers recognised the need for agreement about classification and diagnosis of the illness. As a result groups of experts got together to define the syndrome. The most commonly used criteria has been Holmes et al. (1988) but different criteria were developed in other countries. Holmes et al. (1988) and Lloyd et al. (1988), quoted in Hickie et al. (1990), developed criteria in North America. In Britain, criteria are given in Sharpe et al. (1991) and Dawson (1990), in Scotland by Ho Yen (1990), in New Zealand by McKensie (1988) and in Canada by Whelton et al. (1992). The last two are criteria given in a study, the others are widely acknowledged and are given in detail. Appendix 1 Table 1 gives the Lloyd et al. (1988), Ho Yen (1990), Dawson (1990), McKensie (1988) and Holmes et al. (1988) and Holmes (1991) criteria.

The main differences in these criteria are:-

1) Psychiatric diagnosis.

In Dawson's (1990) criteria, psychiatric diagnosis is only considered as an alternative if it predates the illness, or there are bizarre or inconsistent symptoms or a family history of mental disorder. Subjects were excluded as having CFS by Whelton et al. (1992) if 'there was any underlying primary medical or psychiatric illness'. Ho Yen does not make any such exclusion on psychiatric grounds. Holmes excludes all chronic psychiatric disease including hysteria in Holmes et al. (1988) but excludes only pre-existing

psychiatric disorders in Holmes (1991). Lloyd et al. (1988) do not exclude psychiatric disorder. Lane et al. (1991) discuss the problem of psychiatric diagnosis in CFS. They maintain that CFS is very rare if psychiatric symptoms exclude the subject from the diagnosis and that even excluding those with pre-diagnosed psychiatric disorder is highly suspect since research suggests prior psychiatric disorder may predispose to CFS. The Centre for Diseases Control (CDC) set of criteria by Holmes et al. (1988) was much criticised for excluding all patients with psychiatric problems past or present. Katon et al. (1991) tell us that their patients do NOT meet CDC criteria: only 19 out of 98 did, the majority of the remainder failed to meet the criteria because of current psychiatric referral. The requirement to exclude people with present psychiatric problems was removed as a requirement from CDC in 1990 (Holmes 1991).

2) Onset.

Dawson's criteria requires that there is a definite onset to the disorder and Whelton's criteria requires a flu-like illness at the start of the illness. Ho Yen, Holmes and Lloyd make no such stipulation. This part of the criteria really relates to the previous theories about a trigger to the illness, in other words the belief that the illness is started by a viral illness. This is an argument used in support of organic theories of etiology, that a previously healthy person suddenly becomes ill. However, the presence of a trigger has not been proved to be universal and the Post Viral label has been largely dropped in the UK (Sharpe et al. 1991, Wood et al. 1992). If a proven trigger is a pre-requisite to diagnosis, patients who do not remember onset, as well as those for whom onset was more gradual, will be excluded.

3) Excluded illness and physical testing criteria.

The sets of criteria vary considerably about what they consider excludes a person from CFS diagnosis. There is agreement generally that tests should be made to exclude other conditions, but in some criteria testing is much more extensive. There is clear agreement about exclusion of some illnesses, for example Multiple Sclerosis (MS) and Myasthenia Gravis (MG), but in practise diagnosis is often delayed in these illnesses leaving open

the complication of previously diagnosing as ME (Jelinek 1956), or the diagnosis of MS may turn out not to have been justified (Wookey 1986). For other illnesses their exclusion occurs in only some criteria, for example brucellosis which is specifically excluded in the CDC list given by Holmes (1991). The problem with excluding such illness as brucellosis, infectious mononucleosis, or toxoplasmosis or toxic poisoning is that the triggers of CFS may in fact be excluded and, therefore, exclude a group of patients central to CFS. In the literature some of these illnesses have been reported as causing a fatigue syndrome (chronic brucellosis: Cluff 1991, chronic infectious mononucleosis: Coulter 1988, discussed in Lloyd and Wakefield 1988).

4) Neuropsychological symptoms

Ho Yen (1990) requires the presence of neuropsychological symptoms e.g. memory and concentration problems. Since it is widely debated, and so far not backed up by a body of research, that CFS patients have true neuropsychological deficit this requirement can be considered to be pre-empting a valid debate and prematurely excluding patients.

Considerable differences in the number of patients regarded as CFS arise depending on the use of different exclusions. The psychiatric and neuropsychological symptoms present in any particular CFS population may be dependent on which criterion has been used. Although not as yet reported in full in the literature, Bates et al.'s (1994) study indicates the amount of variation in diagnosis which occurs if different recognised criteria are used for diagnosis.

Bates et al. (1994) show that the same group of patients are diagnosed as CFS at different rates depending on the criteria used. They use criteria from three different countries and, of the 808 patients, 44% are diagnosed CFS under CDC criteria, 62% under the British criteria and 82% under the Australian criteria. Bates also shows abnormal tests to be evenly distributed through the patients diagnosed, irrespective of the criteria used. Thus differences are seen in the numbers diagnosed as CFS, without any particular criteria being superior on the grounds of distinguishing more abnormal or

distinct patients.

### 1.4.6 CFS a diagnosis by exclusion?

Differences in criteria, in the main, revolve around who is excluded from the diagnosis of CFS. The Price et al. (1992) paper shows, as does the discussion of fatigue and viruses in Part one, that the symptoms of CFS occur widely. However Price et al. indicate that exclusion criteria prevent the majority of their symptomatic patients being diagnosed as CFS. The question that should be asked is : Is CFS a diagnosis by exclusion? This would mean that CFS is a diagnosis that is used because of a failure to identify other causes of fatigue and muscle debility. If this is the case, CFS diagnosis is very weak, since positive criteria are a much stronger scientific basis for diagnosis than negative (exclusion) criteria. If it were established that in CFS exclusion criteria rejected 90% of the cases selected by positive criteria, then it may be that CFS does not exist as a separate entity. CFS might simply be an indication of physical or psychiatric illness that has as yet not been diagnosed or is not severe enough for diagnosis.

### 1.4.7 Summary

As a result of failing to find consistent abnormality or test for the condition, diagnosis has been largely by symptoms. The confusion over what is or is not Chronic Fatigue Syndrome occurs over many features even after wide acceptance of Holmes' criteria as a starting point. Problems remain with:

- the inclusion or exclusion of patients with positive testing for an illness;
- the inclusion or exclusion of patients with abnormalities in immunity;
- differential symptom criteria;
- exclusion of patients with similar symptoms but no viral history;
- inclusion or exclusion of currently depressed patients;
- inclusion or exclusion of those with a psychiatric history;
- variability of length of illness considered necessary to confirm as ME or post viral

syndrome;

- the existence of neurological and neuropsychological deficit;

- overlap with conditions such as fibromyalgia or hyperventilation.

Modern criteria for CFS rely heavily on exclusion criteria and this may indicate that CFS overlaps with other medical diagnoses.

As a result of problems with definition, populations defined as CFS may vary widely in their psychiatric and neuropsychological profile. Mis-inclusions may result in people with different illnesses being assessed within the groups. Mis-exclusions may well result in an underestimate of psychiatric conditions.

'The problem of any kind of research into the CFS is that, like backache, it covers a large heterogeneous group of patients in whom physical, psychological, and social factors, may be interacting. Researchers should therefore not be surprised to find that the outcome varies considerably when the aetiology is not more clearly defined.' Shepherd (1992).

## 1.5 CFS and overlapping syndromes

CFS has strong similarities to other modern syndromes and may overlap considerably in symptomatology and definition.

### 1.5.1 Syndromes with overlapping symptomatology

1. Sick Building Syndrome (SBS) is a well documented phenomenon where workers in a particular building complain of a high level of general symptoms. A recent advice bulletin (Kirkton 1990) quotes a 1987 survey of 4000 workers in 46 buildings: 80% of the work force experienced symptoms of ill health associated with their workplace. The five most common symptoms were: lethargy 57%, stuffy nose 47%, dry throat 46%, dry/itchy eyes 46% and headaches 43%. Lethargy and headaches are

prominent complaints in CFS.

2. Allergy syndromes have similarities in symptoms to CFS, notably fatigue. Buchwald et al. (1988) report a study of CFS patients where 50% of patients were found to be reactive to allergens compared to the rate of 15-20% in the normal population. Strauss et al. (1988(a)) find that cutaneous reaction and histories strongly suggestive of atopy occurred in 50% and 83% respectively of their patients tested.
3. Pre-Menstrual syndrome (PMS); the high proportion of women of childbearing age with CFS means that for that reason alone, apart from similarities in the syndromes, premenstrual and menopausal symptoms may overlap with CFS. Symptoms of premenstrual syndrome include complaints about memory and feeling confused; but these are not objectively substantiated (Richardson 1988). One of the most usual symptoms is headache which is a symptom common to CFS patients. Painful joints, allergy symptoms and backache are also common symptoms in PMS.
4. Toxic Poisoning; CFS shares similarities to toxic poisonings of various kinds. Mild symptoms of toxic poisonings, e.g. from industrial paint, are commonly fatigue, poor concentration, irritability and headache. Lehrer and Hoover (1988) compare the symptoms of CFS to cocaine and other substance abuse. Symptoms of cocaine abuse include sleep problems and fatigue, headache, sore throat, nausea/vomiting, depression/irritability, memory and concentration problems, sexual disinterest and panic attacks.
5. Minor/Mild Head Injury (MDI); Post Concussion Syndrome (PCI). This syndrome has a different starting point, head injury, to CFS but is mentioned because of the similarity in symptoms and the similarity in neurological findings. Patients complain of headache, fatigue, dizziness, blurred vision, they are bothered by noise and light, insomnia, difficulty concentrating, irritability, anxiety, memory difficulties and loss of temper. Patients experience slowed reaction time and problems on Stroop and the Paced Auditory Serial Addition Test (PASAT) (Dikmen et al. 1986(a), 1986(b)). Patients' symptoms are regarded as possibly psychological (Rutherford 1979). Dikmen et al. (1989) suggests neuropathological and neurophysiological causes for symptoms, including reduced blood flow, brainstem evoked potentials, and reduced

speed of information processing. The symptomology and neurological findings are similar to those of CFS.

### 1.5.2. Syndromes which may be the same as CFS

1. Fibromyalgia

   Fibromyalgia is a syndrome where muscle pain predominates. The American College of Rheumatology 1990 classification for fibromyalgia is of widespread pain and pain in 11 of 18 tender points on digital palpitation. Fibromyalgia is found as primary or secondary to a concomitant rheumatic disorder. 47% of 100 consecutive rheumatic patients admitted to a Danish rheumatology department meet criteria for fibromyalgia (Rasmussen et al. 1990 in Goldenberg 1991) by examination of tender points in soft tissue. In Sweden 1% of a random population (n=900) were surveyed and found to meet the criteria of fibromyalgia (Jacobsson et al.1989). Sleep abnormalities have been reported in fibromyalgia notably the alpha intrusion noted in slow wave stages of sleep (Modofsky et al. 1984). The similarities between CFS and Fibromyalgia are marked in a study by Goldenberg: he shows 19 out of 27 of the CFS patients studied to have a mean tender point score identical to that of the fibromyalgia patients (Goldenberg 1991). Depression is common in both sets of patients; immunological and pathophysiological changes as well as cognitive changes are reported in both syndromes. In Fibromyalgia certain abnormalities - reduced pain tolerance to electric pulse and the effects of epidural - have led to suggestions that the pain is of peripheral nociceptive-spinal origin. Bennett (1989) suggests that fatigue and physical inactivity lead to unfit muscles which are susceptible to microtrauma and that sleep disturbance might exacerbate this. Muscle strength was found to be diminished in these patients and it was found that muscles did not relax properly after use (Goldenberg et al. 1990). CFS and Fibromyalgia could be the same, or an overlapping, syndrome. The difference lies in whether muscularskeletal pain or fatigue are considered the primary symptom.

2. Hyperventilation

Some recent papers have claimed that CFS is caused by hyperventilation, i.e. overbreathing. Overbreathing occurs in many people but excessive overbreathing can cause impairment of muscle function and other symptoms. Hyperventilation is seen as a medical condition but is closely associated with anxiety. Anxiety states, particularly panic attacks, may bring on overbreathing as patients in such attacks often breath much faster. Rosen et al. (1990) say that 100 consecutive ME patients when tested met the criteria for hyperventilation.

Summary

The diagnosis of CFS is complicated by the existence of syndromes which may be the same illness under a different name, e.g. Fibromyalgia. It is also a syndrome which shares groups of symptoms with other syndromes. The etiology of some of these syndromes is argued to be partly psychological. CFS may also share organic causes with some of these syndromes e.g. toxic poisoning or, in the case of PMS, hormonal disruption.

## 1.6. Who gets CFS?

Introduction

There may be a particular type of person/patient who is susceptible to CFS. CFS patients are thought by some to have more premorbid psychological problems and possibly psychiatric tendencies as shown by the Minnesota Multiphasic Personality Inventory (MMPI) (Stricklin et al. 1990). However, the questions discussed here are: are CFS patients demographically distinctive? and does that give us any other clues about them?

Archer's review (1987) covers some of the main points. Females are up to 10 times more likely to be diagnosed as CFS patients than males. The majority of patients are

from social classes 1 and 2, rarely more than one person in the family has it. Many of those in initial epidemics were medical staff.

### 1.6.1 Sex differences in diagnosis of CFS

The over-representation of women in CFS populations has been widely found. This has been used as an argument for the mass hysteria hypothesis (McEvedy and Beard 1970) based on the idea that young women are more susceptible and neurotic than men. There are, however, other possibilities: it may represent a differential use of the Health Service by women (see later), it could also be to do with greater contact with children; it could be to do with doctors' attitudes to women and their attitude towards the diagnosis of CFS.

Feiden (1990) points out that such arguments are not necessarily relevant because women are generally more prone to autoimmune disorders such as lupus, multiple sclerosis (MS) and rheumatoid arthritis (RA) in which the immune system attacks the body's own tissue. Since some physicians suspect that CFS is also linked to autoimmunity (Lloyd et al. 1988; Klimas et al. 1990; Caligiuri et al. 1987), this sex bias could occur in CFS for the same reasons as in other auto-immune illnesses. The hormonal difference between men and women could also make women more susceptible to the endocrine imbalance sometimes found in CFS (Demitrack et al. 1991 and see Section 1.5).

Another reason for the high number of female patients may be that epidemic ME has tended to revolve around a particular building. These buildings tend to be large institutions where lots of professional people work, with large numbers of female support staff. This pattern shows similarities to Sick Building Syndrome in large new buildings (see "Sick Building Syndrome").

Recent studies in which CFS patients have been sought out from a wide area have shown less male / female bias: Cluff (1991) finds no sex difference, Lloyd et al. (1990(a)) find 1:1.3 ratio supporting the view that the larger female bias found in early studies may be due to other factors than gender difference.

### 1.6.2 Predominance of the middle class in the CFS population

There is a social class bias in the CFS population. Salit's (1985) study suggests that there are more social class 1 and 2 . This class distribution is not however true of all studies, in particular some in which patients have been sought out in an intensive way. For example, in Lloyd et al.'s (1990(a)) study of the symptoms of CFS in Richmond valley New South Wales they find distribution of social class in CFS patients to be similar to that of the community. Ho Yen and McNamara (1991) in a survey of G.P.'s in Scotland finds that 22% of sufferers are students or teachers but only 5% are professional workers (excluding teachers) and 17% are manual workers. This shows that CFS is distributed through the classes although some groups such as teachers are over-represented. It may be that it is the professional person who both seeks out help from the doctor and who is articulate and persistent enough to receive help who finally gets a diagnosis of CFS. The over-representation of professional classes as in Salit (1985) has led to stereotyping of the 'Yuppie flu' sufferer (Shaw 1987).

Alongside the view that CFS is a middle class disease has been assumed that this is to do with a relationship between class and stress. An assumption is made that job stress is associated with the middle class and overstress may cause CFS and this results in the 'Yuppie flu' stereotype. Shafran (1991) discusses this concept and how the ability of the middle class to assert themselves may account for more CFS diagnosis in the middle class. (Stress and how it fits into CFS is discussed more fully later Section 3.4.)

In the studies that fail to show strong sex and class bias, it seems to be that researchers looked at possible patients from a primary source e.g. all in a geographic area or all

G.P.'s in an area. In Lloyds et al.'s case, they looked at all people seeking help for fatigue and decided whether they were CFS, rather than looking only at those diagnosed as CFS by a hospital. This suggests that the pool of CFS patients in the general population has a higher percentage of male and working class people than suggested by data from diagnosed patients.

1.6.3 Work: Place and type of work associated with CFS patients.

In ME's early history, hospitals and schools, and nurses and teachers, are over-represented; this bias still remains (e.g. Durndell 1988, Johnstone 1990). Why should hospital staff be more prone to CFS? There are a number of possibilities: they are more in contact with cause or trigger illness; they are more prone to the suggestion of illness in the case of mass hysteria; they suffer stressors that contributed to the illness.

A Scottish teacher's report in 1992, described ME as a psychiatric illness and suggests that this and other illnesses are due to stress on teachers (BBC 1992). The incidence of CFS has been so high among Scottish teachers that the Scottish Education Department has introduced a new retirement policy for CFS sufferers in teaching; Johnstone (1990) reports that the Educational Institute of Scotland (EIS) claim that at least 200 Scottish teachers are suffering from ME. Stress is not the only possible reason why teachers might get CFS: it could again be a question of contact with trigger illness; the spread of viral illness is high among children in a school environment and it is possible that due to that, or the building environment, teachers are more at risk of CFS.

1.6.4 CFS in children

For a long time it was believed that children did not get ME/CFS; Hill et al. (1959), and Dillon (1978) remark on children in hospital not getting ME when the staff did. Bell et al. (1991) show that children do get ME; adults may be more prone to get it seriously (as is the case with mumps and chicken pox). When children get CFS it seems to be in a

children's epidemic or as a sporadic case. Hill et al. (1959) suggest that, for some reason, puberty might make teenagers and adults more susceptible. It may be that epidemics among children are of a different form.

### 1.6.5. CFS patients and the over-representation of athletes

Amongst high profile cases of CFS, athletes predominate (e.g. David Provan (Shaw 1987), Claire Francis and others (Holoway 1993)). In studies, health workers and the higher professional groups are over-represented (Salit 1985). There appears to be an over-representation of those who have been athletes or keen at fitness pursuits. In the academic literature, Durndell (1988) shows that joggers seem more prone to the illness among academic staff. This could be to do with demographic variables of joggers, i.e. joggers are more likely to be middle class and in the 25-40 age group.

The reason for this over-representation may be to do with personality variables; athletes have been shown to be higher in vigour and extraversion, probably necessary factors in reaching the top (Puffer and McShane 1991). An alternative explanation is that they could be more vulnerable to CFS because they are active (see Literature Survey Section 1.1.3). It could be due to overstrain/stress on the body; over acidosis of the muscle may occur in CFS patients in a similar way to acidosis from athletes overtraining. It could also be due to the athletes' heightened sensitivity of any changes in performance. Puffer and McShane (1991) suggest a cycle of depression caused by obsession: a slight downturn in performance leading to a slight depression in mood leading to further poor performance. In this scenario depression and poor performance can lead to symptoms and to chronic fatigue. Morgan et al.'s (1988) study shows that inadequate muscle glycogen stores in athletes due to overtraining correspond to mood disturbance. The result of overtraining therefore may be a mood and muscle problem. In respect of type of profession and athleticism, Durndell (1988) shows this is not just a question of professional athletes being at increased risk but also regular joggers.

### 1.6.6 The age profile of CFS patients.

There appear to be peaks in the age profile of CFS patients: Ho Yen and McNamara (1991) report an age peak at 35-39 in male patients and in female 25-29 and 40-45. The suggestion has been that stress could cause these age peaks (see Brozovic 1989): age 25-29 in women is a time when many women are coping with new married life and working or coping with small children, or both, so that they are very busy and have a number of, sometimes conflicting, demands (Malley and Stewart 1988). Interestingly, Stricklin et al. (1990) does not find that 'epidemic neuromyasthenia' female patients scored any differently on the Meharian Achieving Tendency Scale for females than controls; higher achieving tendency might have supported this model. It is harder to produce an equivalent argument for the male patients but 35-39 can be suggested as a time when a man is stuck where he is in his career, his career is at its most demanding etc. For examples of this type of explanation of illness and stress to the patients in relation to women see Brozovic (1989) and assumptions made in Rose et al. (1990). As yet there is no real evidence that stress is a cause of CFS; however it could fit into an argument that CFS is related to psychological profile as discussed later.

There are other possible reasons for this age distribution. Both sexes are very active in the 20-40 period in general and their responsibilities may mean they are unable to take proper time off at times of illness or for recuperation. Hormonal disruption, as may occur in CFS (Demitrack et al. 1991) may be most upsetting to body systems at this sexually active stage and particularly for childbearing or pre-menopausal women (see section on "PMS" in 1.5.1).

### 1.6.7 Discussion of demographic profile in general

It is possible that the demographic profile of the CFS patient represents the stereotype Type A personality: highly intelligent, overstriving, slightly obsessive and pushing themself hard, as the high achieving athlete needs to in order to make it to the top

(Holoway 1993). Abbey and Garfinkel (1990) relate this stereotype to illness: 'The achievement orientated personality style theoretically places individuals at risk for depression and protracted disability'. Another suggestion is that people caring for others overstretch themselves to meet demands, as with teachers, nurses and mothers with small children. This type of stereotype is not maintained in regard to class and sex in new intensive studies (Lloyd et al. 1990(a); Petersen et al. 1991) but the activity/athletic level of patients does seem to be high (Durndell 1988). It may be that the fashion for activities such as jogging among the middle class is the key to this distribution. One major argument for a middle class bias in diagnosis is, however, utilisation of the health service.

### 1.6.8. Health utilisation

In order to be diagnosed as CFS/ME/PVFS formally, the subject needs to be seen by the health services. The rate of diagnosis of any disorder can be biased by who is using the service. If CFS is widespread in the community, as surveys such as Lloyd et al. (1990(a)) and Petersen et al. (1991) suggest, then the inequality of diagnosis may depend on who goes to the doctor, their persistence, and the doctors' reaction to them.

Ham (1990) sums up the evidence of demographic inequality in use of the health service in a quotation by Stacey: "There is evidence, first, of continuing and perhaps increasing class differentials in death rates (more in the lower class); second, of more illness in lower than in higher classes; third, that the health services are more available to the middle classes than the working classes; fourth, that the middle classes use the health services more than the working classes; and, fifth, they get more out of them when they do use them" (p. 898).

So a middle class CFS patient is more likely to go to a doctor than a working class one, and more likely to get a diagnosis if he/she does. The diagnoses of CFS may be related to those who persistently use the health service rather than just a cross-section of those

who have the symptoms.

Williams et al. (1990), looking at the U.K. Second National Morbidity Survey, point out that females' highest rate of utilisation of health services is at age 25-44 (which fits in with CFS age profile) and for men 46-64 (which does not). They also point out that women use the health service more than men. Married women use the health service more than single women and single men more than married men. Lewis and Wessely (1992) write: "It has been suggested recently that the apparent positive social class bias in hospital studies is the result of differences in health care utilisation."

Anderson's model of health care as summarised in Williams et al. (1990) suggests many factors influence utilisation of the health service, as shown in diagram Appendix 1 Table 10. Apart from cost, which is not so relevant in the UK, he points to predisposing factors, demographic and belief structures, and the perception of illness level.

Koff et al. (1990) in looking at health care utilisation come to the conclusion that "psychologically distressed persons appraise their global health status less favourably than non distressed persons, have more functional disability and may have a higher incidence of chronic disease". According to Koff et al., health-care structures may encourage dysfunctional illness behaviour. Thus, if CFS patients are psychologically disturbed, this is more likely to lead them to health care whatever the degree of symptomatology. Therefore CFS patients, in whom depression and anxiety are high (see next section), are more likely to seek health care than if they were not psychologically affected. Spilken and Jacobs (1971) state that results of their study on stress coping and illness seeking behaviour show "premorbid indicators of unresolved life stress accurately predict who will seek care for illness", i.e stress may lead to health utilisation.

Cluff (1991) finds that those who developed CFS sought medical care more frequently, prior to the syndrome, than those who also had a 'trigger' illness like Coxsackie B and did not develop the syndrome. This suggests that oversensitisation to physical stimuli,

as well as belief in the health service, may influence whether a person goes to see a G.P. Cluff (1991) also comments that women tend to utilise health services at least twice as much as men; hence, patterns of differential use of the health service by sex may account for part of the sex difference in CFS diagnosis.

Men are less likely than women to seek medical help and they are even less likely than women to receive a psychiatric diagnosis. Married women are the most likely group to receive psychiatric diagnosis. If CFS is thought of as showing psychiatric problems it may also follow that a diagnosis of CFS may be made more frequently in women.

According to Ho Yen (1990), CFS patients take up a lot of G.P. time and medical care seems to have little to offer them. The high rate of depression and anxiety in the group leads doctors to suppose that their general symptoms may be the result of psychological distress rather than illness. Wessely (1990(b)) and others take the approach that mental health care might have more to offer than general heath care.

### 1.6.9 Summary

The chances of being diagnosed as having CFS are greater if you are female, in the medical profession, in the professions that work with CFS sufferers, work in the same building as people who are CFS sufferers, or have done a lot of sports/exercise. The reasons for this distribution could be exposure of CFS patients to a particular environment or contagious element. Alternative psychological explanations include the patient's personality type, vulnerability to stress, hysteria or somatisation leading to, or predisposing to, developing the syndrome. On the other hand it may be that the diagnosis is restricted by factors such as health service use and distribution of services, or persistence of the patient.

These risk factors in getting CFS are displayed in the following diagram (Figure 1). Demographic and geographic variables have already been shown to increase one's risk

of getting CFS. The diagram also includes personality variables which are discussed in the section (3.1) on psychiatric aspects of CFS. In the diagram one can see that the reasons for being at risk of CFS are both individual and situational.

### 1.7 Recovery from CFS

CFS is an illness which as discussed earlier may be long term. The evidence suggests, however, that most people recover over time without any intervention. Clare (1991) describes ME: 'the syndrome in different patients follows a similar course with frequently a distinct beginning (usually moderate illness) followed by gradual recovery with relapses that decline in frequency'. Strauss et al. (1988(b)) show an effect of placebo treatment in CFS patients, in research over some months, of 41% recovery, and they estimated a 20% spontaneous recovery rate. It is likely that the placebo rate generally in CFS reflect an element of spontaneous recovery.

It is extremely important to realise, in the light of claims to be able to cure CFS, that spontaneous recovery occurs at a high rate. Therefore spontaneous recovery should be controlled for in any study of 'a cure' for CFS. It is important that all longitudinal studies of CFS take into account improvement over time.

### 1.8 Summary of Section 1

CFS is a syndrome the definition and diagnosis of which is varied. Physical tests for the syndrome are not available; e.g. viral screening for Coxsackie B etc is inconclusive. Therefore diagnosis is largely by symptoms, with exclusion criteria accounting for a large rejection of symptomological cases. Symptoms are mainly those found in high rates in the community. CFS patients are disproportionately white, female and middle-class and are likely to work in the caring professions or teaching.

# NEUROPSYCHOLOGICAL AND PSYCHOSOCIAL ASPECTS OF CHRONIC FATIGUE SYNDROME

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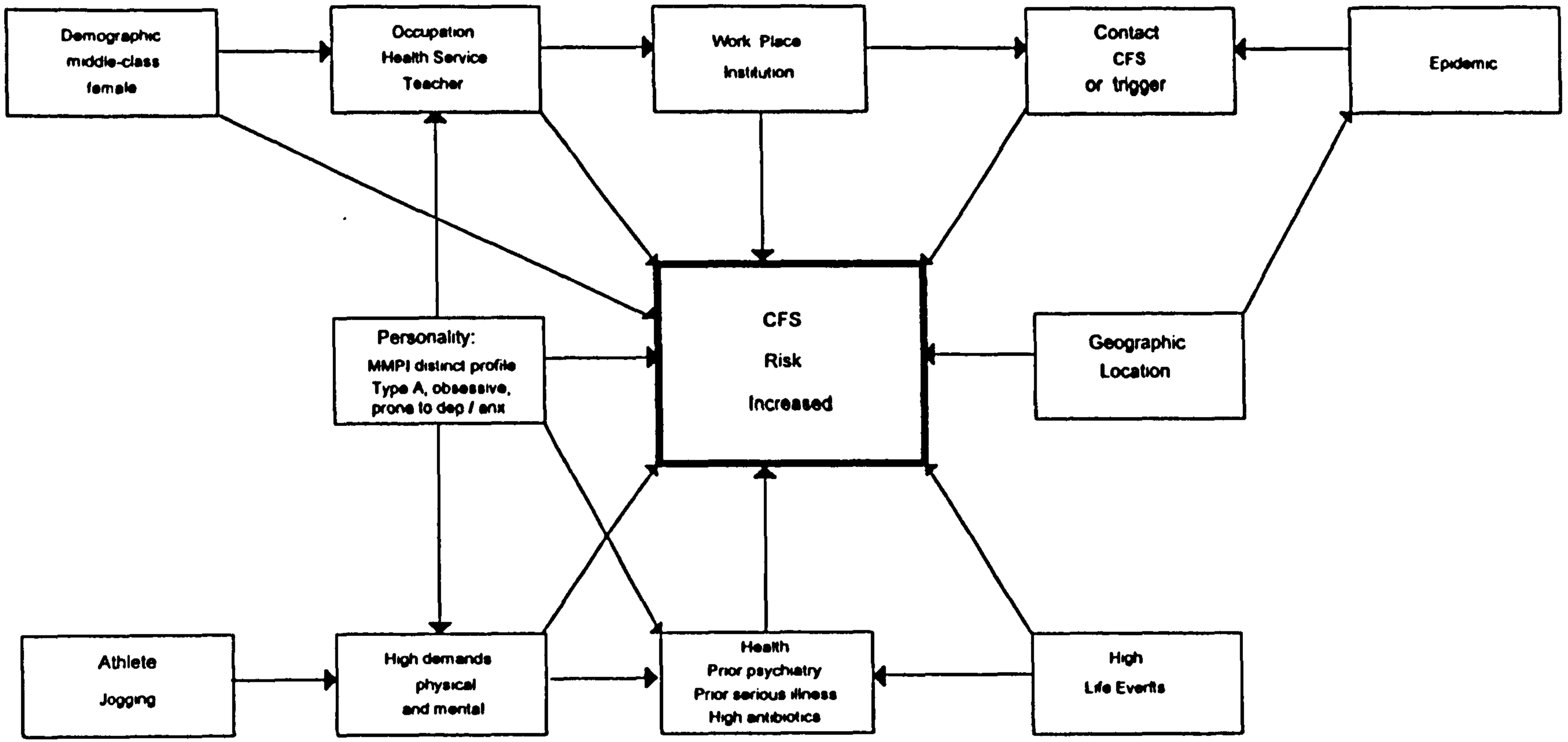



**Figure 1: Vulnerability to CFS**

Explanations of CFS range from wholly organic to wholly psychological explanations. Overlapping syndromes suggest hormonal, allergic or toxic influences as well as those suggestive of viral or psychological origin (stress or depression). Komaroff (1992) suggests a model of CFS pathogenesis (shown in Appendix 1 Table 9) which takes account of these factors.

## 2. History of CFS/ME

### 2.1 Early epidemic ME

The literature starts with reports of a series of outbreaks in the wake of polio epidemics, the bulk of them in the 1950's. The Lancet leading article of May 26th 1956 ("A New Clinical Entity" 1956) reports a small outbreak in 1917 (von Economo) and one of 5000 cases in England and Wales in 1924, but in the following years cases were rare. An epidemic occurred in Los Angeles in 1934 and three epidemics were recorded in Switzerland 1937 to 1939 (Parish 1978(b)). Retrospectively some other illnesses have been claimed to be M.E. Included in these are the 1918-19 outbreak of swine fever (Ho Yen 1987) and the 'effort syndrome' treated at Mill Hill during the Second World War mentioned by Richter (1978). The list of epidemics in the decade following the Akureyi outbreak in 1948 (Sigurdsson et al. 1950) demonstrates a mushrooming of the problem (see Appendix 1 Table 3 for list of early epidemics). This crop of epidemics at the one time might be explained by: the emergence of a new illness, an increase in prevalence of an illness, or a change in perception/diagnosis of illness (one argument for the third is that ME is not found in the third world - see below).

Myalgic Encephalomyelitis, as it became known, was brought to the attention of the British public by an outbreak which caused the closure of the Royal Free hospital. The epidemic among the hospital staff occurred between 13th July and 24th August 1955, when 292 members of staff are known to have been ill and 255 were admitted to hospital. The patients experienced a period of initial illness, sometimes severe, when

symptoms of encephalitis and paralysis could be present, and it involved high morbidity in patients for months or, in some cases, years. Some of the cases were mistaken for poliomyelitis which was epidemic in the community at the time of the ME epidemic. Compston (1970) maintains that organic involvement of the CNS was indicated. Muscle wasting was rare despite the prominence of muscle pain.

The Royal Free epidemic is typical in many ways of early epidemics. It occurred in an institution, it followed a wave of polio, patients often had acute symptoms sometimes mistaken for encephalitis in the initial stages and it was accepted by physicians in attendance as an organic illness of unknown etiology. Crowley, Nelson and Stovin (1957) show the degree of spread of illness in the Royal Free epidemic (Appendix 1 Table 4). They report several cases outwith the hospital among relatives and friends. Their examples suggest to Crowley et al. an incubation period of between 5-7 days (see Appendix 1 Tables 4 and 5 for progress of the epidemic (Crowley et al. 1957)). Although early outbreaks of ME are usually associated with epidemic ME, sporadic cases were also reported in the North London area around the time of the Royal Free epidemic (Compston et al. 1970).

The epidemics that followed these original outbreaks were defined by comparison with the previous epidemics. For example 'an illness with features in common with what has become known as epidemic neuromyasthenia (called EN by Acheson 1959; Henderson and Shelekov 1959; Parish 1978(b)) affected the staff of the hospital for Sick Children, Great Ormond Street, London between August 1970 and January 1971' (Dillon 1978). Definition was therefore by epidemic. Dillon defines the epidemic by giving place and time, and little notice was taken of sporadic cases. The early epidemics were identified by virtue of similarity of occurrence:

1) the illness occurred in similar way, i.e. epidemic;

2) the illness occurred in institutions, mainly hospitals;

3) the illness followed a recognised polio epidemic;

4) symptoms were carefully recorded and compared to earlier outbreaks.

## 2.2 McEvedy and Beard

An important break in the literature occurred after the reinterpretation of the key Royal Free reports. In 1970 two psychiatrists, McEvedy and Beard, wrote a paper based on the data from the Royal Free epidemic (McEvedy and Beard 1970 and 1973). They place great emphasis on the type of patients that were ill in the epidemic and argue that the epidemic was an outbreak of hysteria. This is discussed more fully in Part 3.2.1.

## 2.3 G.P.'s reports of sporadic illness

In the late 70's and 80's reports of a fatigue syndrome which was claimed to be the same illness came from General Practices. However they did not fit the points of similarity stated above defining epidemic CFS/ME. The extent to which these new outbreaks had moved away from the defining limitations of the early literature is pointed out in the differences below:

New outbreaks

1) were not necessarily epidemic;
2) were not necessarily clustered in the places of work or residence;
3) patients' reported symptoms were now more chronic and generally less serious;
4) the illness now followed a number of different viruses.

For example, Corridan (1978) describes in detail patients from different areas of SW Ireland as a group with 'epidemic neuromyasthenia'. He describes the symptoms as 'fatigue, pallor, headache, neck pain, alterations in mentation, dizziness, nausea and vomiting, paraesthesia, weakness and heaviness of limbs and a prolonged relapsing course". He goes on to describe each patient in detail over a period from February to September 1976.

The later papers were mostly from General Practitioners; they describe fatigue and muscle fatigue over a period of time with additional symptoms such as sleep disturbance,

depression and cognitive complaints. They are concerned with the prevalence of the illness and its links to glandular fever and Coxsackie B. Keighley and Bell (1983) report 20 (out a practice with 2500 patients) with suspected ME, 16 of whom had high Coxsackie titres. Buchwald et al. (1988) find that 21% of 500 unselected patients between 17 and 50 who sought primary care for any reason were suffering from a chronic fatigue syndrome, and a significantly greater number than among controls had a history of mononucleosis. Both subjects and controls showed evidence of past EBV infection.

The new reports started a whole new impetus to research CFS, the results of which are described elsewhere. The difference between early and late reports also lead to discussion as to whether the two bodies of literature describe the same illness.

**2.4 ME and CFS: two different illnesses ?**

The difference between the late and early reports has led to two suggestions:

1) that these are two separate illnesses;

2) that the illness has changed.

The simple division between early ME and current CFS has several problems. Although the bulk of reports of early epidemics was followed by a relatively quiet period the time gap may be artificial for the following reasons:

1) The early 1950s reports come from hospitals; those of the later 1980s come mainly from GPs; because the groups reporting the illness are different this may account for the difference in the type of symptoms reported. Hospitals, although reporting patients who were staff, still tended to see acute patients with the initial illness; G.P.s see patients over the long period of chronic disability following.
2) Outbreaks of CFS/ME occurred during the 60's and 70's even though they were not so well reported (Dillon, 1978; Corridan, 1978; Behan, 1980). Therefore a separation by date of illnesss may be invalid.

3) Epidemics and large groups of patients within a building still occurred after 1970 (Durndell,1988; Buchwald et al.1992) and sporadic ME before 1960 (Scott, 1970).
4) Severe cases have been reported in the literature since the 1970's (Longden, 1989; "Believe M.E." 1992; MacIntyre, 1993). In view of this, this review has included both pre-and post 1970 literature.

# 3 Neuropsychology of CFS

CFS is an illness which is imprecisely defined and for which etiology is uncertain. It has already been indicated that the risk of getting CFS may be related to demographic and psychological factors. This Section looks in detail at the psychology and neurology of CFS; both the evidence of their influence and theories of how they affect CFS.

## 3.1 Depression and CFS

### 3.1.1 Evidence for depression in CFS patients

Kendall (1967) was the first main study to report serious psychiatric sequels to ME and he reports that they appeared not to have a prior psychiatric history. Taerke's study in 1981 (Taerke et al. 1981) was one of the earliest to show, in a properly designed study, an association with depression. His results show 67% of ME patients fulfilling criteria for major depression compared to less than 20% of the control group. He also states that 50% of the patients had a major depressive episode prior to developing ME. Kruesis et al.'s (1989) study shows similar results: of CFS patients, 75% had depression and 67% had predated psychiatric problems. Wood et al. (1991) describes a comparative psychiatric assessment between CFS and patients with muscle disease; they show that the CFS group have a higher fatigue inventory score, hospital anxiety and depression scale score, higher Spielberger trait anxiety and state anxiety, and are more likely to have seen a psychiatrist since the onset of their illness, have a relative with psychiatric history and say they had had a past psychiatric episode. They report that at least 26%

of the CFS patients had a significant past psychiatric history. These studies' results agree that CFS patients score highly on depression and anxiety.

### 3.1.2 Methodological problems in data used in depression studies

The main problem with many of these studies is that they rely on a retrospective recall of symptoms from patients or medical notes. This has methodological problems.

1) Researchers looking at old material may inappropriately re-interpret past symptoms (e.g. interpret as major when they were minor) or be selectively biased in their interpretation.
2) Memory of the normal subject is selective and tends to suppress negative events but in the case of depressed individual may be more likely to produce more negative events. (A review of the literature leading to this conclusion is given in Baddeley (1990) Ch 15).
3) The patient, but not the control, is seeking meaning for their illness and is likely to produce more events (usually negative) to explain the illness (Baddeley 1990; Blaney 1986). Martyn (1990) comments that patients have a 'natural interest in trying to understand why they have become ill'.
4) The subject is inaccurate in recalling when events take place and therefore whether they are appropriate to the timescale given by the researcher or even whether they are before or after the start of the illness (Davies 1992).

### 3.1.3. Difficulties in understanding the meaning of a depressed score in CFS

There are other problems in testing for depression in CFS.

1) Somatic symptoms of depression overlap considerably with symptoms of CFS. Cavanaugh et al. (1983) and Ray (1991(b)) find that items such as fatigue, weight loss and worry about health do not discriminate between psychiatric and medical patients. Somatic questions accounted for 31% of questions on the Hamilton Depression Scale and 33% on the Beck Depression Scale even though,

theoretically, these scales are cognitively rather than somatically based. In CFS, fatigue, sleep disorder and other symptoms are present which are also characteristic of depression. This may mean CFS patients are depressed, but if they are not they are still likely to score high on most depression ratings.

2) There is disagreement as to what constitutes a depressed score on some scales. CFS patients tend to score higher than controls but these scores are often not in the clinical range. Petersen et al. (1991) in the Minnesota study find that 48% of patients had elevated scores on three psychometric screening tests and so sent them for psychiatric assessment. They state that in none of these cases could a DSM-III diagnosis explain the patient's illness and depression which, when present, was usually determined to be an adjustment disorder (reactive depression) precipitated by the typically acute onset of CFS. The mean and standard deviation on the Beck Depression Scale was 15.4±8.6, which is in the mildly depressed range.
3) Depression is known to be high in endocrine, metabolic and nutritional disorders and even some neoplast diseases (Ray 1991(b)). As discussed in section 1, CFS illness shows associations with thyroid illness, and thyroid illness symptoms overlap with depressive symptoms; these depressive symptoms often resolve with treatment (Szabadi, 1991).
4) The viral illnesses with which CFS has been associated (see viruses section 1.3.4) have also been known to cause severe depression (Abbey and Garfinkel 1991).

### 3.1.4. Depression in other chronic conditions

Severe psychiatric and depressive symptoms have been seen in herpes virus but often cease with treatment and recovery from the illness (Crow 1978). The diagnosis of depression is often withheld where a medical condition is known. Depression is high in chronic conditions in general and the general predisposition to illness may well be increased by depression. Katon et al. (1991) compare consecutive Rheumatoid Arthritis (RA) patients with CFS patients (their criteria are based on Holmes but including psychiatric factors). Katon et al.'s (1991) results show 70% of ME patients are depressed

but also 41% in RA (and 32% in diabetes in other studies). Katon et al. also find CFS patients to be higher on all psychiatric categories. However, the scores for both sets of patients are high and the length of illness varies considerably between groups. Dakof and Mendelssohn (1986) quote studies of Parkinson's disease patients showing a 12-52% depression rate (most between 30-40%). In three separate studies they comment that Parkinson's disease patients are significantly more depressed than patients with other diseases and more disabling diseases; they conclude that the depression may be part of the illness.

Ray (1991(a)) suggests that CFS patients may be particularly prone to depression because they have severely limited their activity and social contact and because of the ambiguity about their illness which has a direct effect on coping (she quotes Shalit 1977 in support) and the difficulty they have in obtaining recognition for their illness (she quotes Gadd 1989 in support). The stage and the status of the illness may have a profound effect on depression. CFS patients have to cope with disbelief in the reality of their illness, more uncertainties about nature and duration, and more difficulty with employers etc. 'There is growing evidence that in chronic illness of all kinds, psychological disturbance is generally greatest in the early stages of the illness' Dakof and Mendelssohn (1986). Difficulties in adjusting to CFS due to delays and uncertainty in the diagnosis of CFS may increase this early depression.

### 3.1.5 Differences between CFS and depressed patients

Differences between CFS and depressed patients have been noted in some papers: Smith (1991) considers that differences in results on visual illusion tasks between ME patients and controls distinguish them from depressed or functional patients. Prasher et al. (1990) state that delayed P 300 evoked potentials found in ME patients are not found in depressed patients. Perhaps more pertinently, Taerke et al. (1987) find the Dexamethasone Suppression test, which is used to test for depression, not to back up the findings that CFS patients are depressed (Taerke 1981, Ray 1991(a)).

### 3.1.6 Antidepressant treatment in CFS patients

Treatment of depression in CFS patients, particularly drug treatments, have had mixed results: some reports actually say they have harmful results, more that they appear ineffective and some psychiatrists claim to be able to help all CFS patients in this way (see Shepherd 1992). Early reports of the use of antidepressants, e.g. Parish (1978), suggest that they exacerbate ME. Miller et al. (1986) hypothesise that certain tricyclics may inhibit cell-mediated immune response. Gantz and Holmes (1989) warn that monoamine oxidase (MAO) inhibitors must be administered carefully but cite successful studies using MAO inhibitors. Dowsett and Ramsay (1992, p289) claim treatment with antidepressants to be ineffectual in those patients who were so treated, about 29% of patients treated that way recovered. This is very low when one considers that the spontaneous rate of recovery in CFS patients may be over 20% (As already stated Strauss et al. (1988(b)) show a placebo rate in CFS patients in research over some months of 41% and they estimated a minimum 20% spontaneous recovery rate). Lynch et al. (1991) outline the use of antidepressants in CFS. Lynch refutes that there are systematic observations of problems in antidepressant therapy and advocates lower rates of dosage and slower rates of increase in dosage to prevent problems such as increased sedation. Lynch reports 67% of 30 CFS patients responded well to antidepressant therapy in terms of depressive symptoms. Lynch, however, says improvement is not universal and does not necessarily mean an improvement in fatigue and myalgia. Wessely (1990(b)) mentions that Kleinman (1992) reports 65% success with tricyclic antidepressants given to neurasthenia patients, and Jones and Miller (1983) report a 70% success rate treating CFS patients with tricyclic antidepressants , but describes these reports as 'anecdotal'. This could also be said of the ME Associations study (Shepherd 1992) and that reported by Ramsay and Dowsett (1992). Goldenberg et al. (1989) show in fibromyalgia good effects with a combination of tricyclic antidepressant drugs and Naproxen, an anti-inflammatory drug. This might be effective therefore in CFS.

Antidepressants have not, however, emerged as a cure for CFS: Shepherd (1992) writes, 'Although these drugs clearly have a role in patients with co-existent depression a much larger survey of 336 patients found out that overall they were no more effective than therapeutic nonsense such as a regimen to eliminate candida'.

### 3.1.7 Summing up of 3.1

CFS patients have a high level of depression score on testing (see para 3.1.1) and some studies indicate a high level of pre-illness psychiatric history in the CFS population. Depression may be present as part of the syndrome or as cause of the syndrome, or both. Ray (1991(a)) says that 'The presence of psychological symptoms does not in itself indicate that a disorder has a psychological basis though the existence of depressive symptoms implies that the disorder may involve processes which are in some way linked to depression'. Even if depression is linked to CFS causally, it is more likely that it is part of a complex process including a number of assaults on health by problems of environment and lifestyle, rather than that it is a sole factor.

## 3.2. Psychiatric Indicators in CFS

### 3.2.1 The Hysteria hypothesis

McEvedy and Beard (1970(a) and 1970(b)) review the notes of the Royal Free epidemic and come to the conclusion that the outbreak was due to mass hysteria; one of the main reasons for their conclusion is the glove and stocking anaesthesias found in 15 of the severer cases and the lack of objective evidence of physical abnormality. McEvedy and Beard's explanation is not accepted by a number of the neurologists involved (Compston et al. 1970). McEvedy and Beard (1973) look at 15 other epidemics and suggest that 8 are also hysteria, 6 observation of normal ill health in the community and one a different illness. The reasons for hysterical epidemics they suggest include 1) a rising level of anxiety due to polio; 2) a concentration of medical examination on the nervous

system, (points (1) and 2) caused altered medical perception); 3) stress caused by overwork in an epidemic of polio; 4) doctors being over-anxious to examine symptoms in case the patient had polio; 5) a susceptible population i.e. young and female. In a later paper McEvedy and Beard (1973) suggest that these females had pre-illness personality and psychiatric problems.

McEvedy (Moss and McEvedy, 1966) had already done research into hysteria and had published a paper about hysteria in a girls school. His arguments were widely accepted. There are other documented cases of widespread illness amongst a tight knit population which appear to be hysterical, for example in 'the June Bug' (Kerchkoff and Back 1968). CFS has also been associated with Da Costa or Effort syndrome (Hyde 1992(a)) which is also thought to be hysterical.

Compston and colleagues from the Royal Free (Compston et al. 1970) objected to McEvedy and Beard's interpretation and point to: laboratory examinations showing morphology of lymphocytes in a substantial proportion of the patients and abnormal EEG; symptoms such as fever and palsies as well as lymphadenopathy. They also point out that this case is considerably weakened by evidence of concurrent sporadic ME in North London at the same time.

Acheson (1959) points out that similarities in the cases in Los Angeles in 1934 and the Royal Free in 1955 were unlikely to be due to preconception on the part of medics as argued by McEvedy and Beard (1970). Acheson (1959) argues that the Los Angeles epidemic was not known about in detail at the Royal Free. More importantly the patients were originally thought to be suffering from two different illnesses - in Los Angeles infectious mononucleosis, and in the Royal Free poliomyelitis. They were also treated by different specialities: orthopaedic surgeons in Los Angeles and general physicians and neurologists in the Royal Free. This has been a common pattern in the history of ME/CFS that despite changes in the syndrome over time, similarity in cases at first attributed to different causes has occurred.

### 3.2.2 Neurasthenia and CFS

Wessely (1990(a)) maintains that CFS is not a new illness, it is neurasthenia under a different name. Neurasthenia is a syndrome with fatigue as a primary symptom (Wessely 1990(a), Beard 1869). Beard (1869,1880,1881) described the symptoms of neurasthenia in eight categories: general physical exhaustion, mental exhaustion including memory and concentration difficulties, muscle spasm and pain, morbid fears, insomnia, autonomic nervous system signs, sexual symptoms, and other symptoms including gastric, nausea, balance and visual problems. These symptoms are strikingly similar to CFS. Neurasthenia was thought originally to have an organic base, and as for CFS a standard treatment was rest. As with CFS it affected mainly the professional classes. It was later accepted as psychosomatic/hysteric, possibly due to environmental stresses. The Diagnostic and Statistical Manual III of the American Psychiatric Association (DSM-III American Psychiatric Association 1980) classify it under dysthymic disorder, a term for a disorder of a psychosomatic nature.

### 3.2.3 Psychiatric Tests and CFS

A more comprehensive exploration of general psychiatric symptoms in CFS has been carried out by Blakely et al. (1991). It has the advantage of comparing CFS patients with chronic pain (CP) patients. It shows more similarity on the GHQ between CFS (7.9) and CP (7.1) than normals (1.9). In the Minnesota study (Petersen et al. 1991) MMPI clinically significant abnormal results were found in 84% of CFS patients, 47% of Chronic Pain (CP) and 12% of controls. In CFS and Chronic Pain groups high numbers of people were assigned to hypochondrias/depression or hypochondrias/hysteria categories when rated according to the MMPI. It is suggested that CFS might be a subset of chronic pain. CFS patients also scored higher on anxiety, neuroticism and emotionality than CP patients, and CFS patients showed a tendency to direct hostility inwardly. CFS patients are shown to have higher anxiety levels than CP patients, but lower social dysfunction.

Stricklin et al. (1990) examine epidemic neuromyasthenia (NM) patients diagnosed by public health physicians in America. These NM patients have CFS type illness but are categorised under an older diagnosis. Subjects were tested on the MMPI, and NM patients score much higher on the MMPI in general. Scores of NM patients show a different pattern of performance indicating depression, tension, anxiety, social withdrawal, abulia, stress, somatic discomfort, unhappiness, physical fatigue and exhaustion, feelings of helplessness, confused thinking and self doubt. As previously noted this study also finds a difference on life events but none on the Mehrabian achievement scale for females. Stricklin et al. also say that comparison would have been best done with a chronically ill group.

Manu et al. (1988) find that of 135 referrals to a fatigue clinic, 67% have psychiatric diagnosis, 3% have medical diagnosis, 5% CFS and 25% no diagnosis. Wessely and Powell (discussed in Wessely 1990(b)) study 47 referrals with unexplained fatigue to a specialist neurology clinic using the Schedule for Affective Disorders and Schizophrenia. Results classify patients as follows: 50% major depression, 2% conversion disorder, 4% anxiety disorder, 2% phobia, 6% minor depression, 13% somatisation and 23% had no psychiatric diagnosis. In all three studies, one may not be showing CFS patients as psychiatric patients but may be showing CFS sharing symptoms with other fatigue states and psychiatric states. These studies may be looking at different patients from CFS patients since strict criteria are not given and a different name is used. Appendix 1 Table 13 shows a breakdown of psychiatric results in CFS (taken from Buchwald 1992).

Smith (1991) finds CFS patients (n=83) score higher than controls on the Middlesex Hospital Questionnaire for anxiety, somatic symptoms and depression.

Summary of 3.2

CFS patients do not present with a clear personality profile. Psychiatric indicators that have been different to controls in CFS studies suggest a tendency to depression, anxiety,

hysteria and somatisation in CFS patients.

### 3.3 Psychosomatic indicators in CFS patients.

Why is the syndrome CFS often regarded as psychosomatic?

(1) Symptoms of CFS are general, they involve many body systems and are, in most cases, unverifiable (Grafman et al. 1991).

(2) Disability and invalidity exceed that expected according to their symptoms (Portwood 1988).

(3) CFS patients are generally more depressed and anxious than normal controls (Taerke et al. 1987).

(4) CFS patients often appear to live an unnecessarily dependent lifestyle due to (2) above (McEvedy and Beard 1970(b)).

This view is supported today in the following which suggest CFS patients overestimating illness.

Stewart (1990(a); 1990(b)) suggests that CFS patients are often patients who attach themselves to the latest fashionable illness. He maintains that this is proved by taking a sample of medical records of such patients that have claimed to be suffering from total allergy syndrome or PMT or other well publicised modern illness prior to claiming to have CFS. This, of course, does not take into account that these illnesses may have similar non psychological origins, or that these previous diagnoses might be part of an attempt to diagnosis the same syndrome.

Digon, Goicoechea, and Moraza (1991), Spanish doctors, complain that now CFS is receiving publicity in Spain, they expect more people to present themselves as sick with CFS because they put their symptoms into this context. Furthermore, the symptoms they have will be greater than they would have had because of this belief.

Membership of a support group is associated with poor outcome in CFS (Sharpe et al. 1992); this may be because it is the more severely ill who join or it could be because the support group encourages people to believe they will be slow in recovering.

The problems with taking a psychosomatic view of CFS are:

1. Historically many illnesses have been viewed as psychosomatic when they are not well understood, including Tuberculosis (Ray, 1991; Dakof and Mendelssohn 1986).
2. There may be a trend to over-psychosomatise illness, particularly in women, at the present time (Gouldsmit and Gadd 1991; Brozovic,1989; Lennane and Lennane, 1973). There is evidence of a high proportion of psychiatric patients who may be suffering from organic rather than psychiatric disorder (Hall et al. 1981; Koranyi, 1979).
3. Doctors familiar with patients prior to their illness have reported that the psychosomatic diagnosis is inappropriate (e.g. Judge 1970).
4. Judgements as to (2) and (4) above may be subjective and indicate that the extent of the illness is not fully appreciated. Secondary gain in CFS patients is disputed for example by Hartnell (1989) and Salit (1985).

## 3.4 Stress, life events, locus of control and CFS patients.

### 3.4.1 Stress in CFS

Studies looking at stress in CFS patients show weak relationships between life events and CFS. Wood et al. (1991) find 32% of CFS patients have a major stressful life event in the six months prior to their illness. Stricklin et al. (1990) find significantly more life events in CFS than controls prior to the illness, mainly due to bereavements of close relatives. Psychiatric examination of CFS patients reported later suggest that they rated high on neuroticism and emotionality (Blakely et al. 1991); they were also depressed and anxious. Powell et al. (1990) show that CFS patients tend to attribute their symptoms to an external cause while a depressed group tend to attribute them to internal causes:

these factors could make them vulnerable to stress. On the whole the area of stress and CFS still needs to be more thoroughly examined.

The assumption that stress makes one vulnerable to illnesses like CFS is based on evidence. Research has indicated a link between immunosuppression and stress. Solomen et al. (1979) discuss how experiments on rats and other animals link stress produced in the laboratory with t-cell function, neurochemical and hormonal changes and further suggest links with tumours in human beings.

Greene et al. (1978) show a link between the Profile of Mood States (POMS) life change units and a decrease in lymphocyte cytotoxicity; they hypothesise that the POMS high vigour score leads to denial which is used as an unsuccessful coping mechanism in the face of increased stress. Locke and Hurst (1978)'s study shows a correlation between high stress, poor coping and a decline in killer cell activity; this is the type of immune dysfunction found in CFS.

The hypothalmic-pituitary mechanism is thought to be the link between psychological processes and Central Nervous System (CNS) changes (Arnason 1991). The pituitary-hypothalmic mechanism has been shown to be abnormal in CFS (Demitrack 1991).

The role of stress is problematic because a lot of people who are heavily stressed do not become ill. Kobasa (1979) suggests that over 75% of highly stressed individuals are in this category. Kobasa looks into the differences between the stressed ill and the stressed not ill and shows locus of control and powerlessness, alienation from self and poor positive response to challenge to be very important in increasing the likelihood of becoming ill when stressed. The most highly significant differences between those with symptoms and those without are related to their perception of stress. In today's society, if stress is part of our fast lifestyles, response to stress is probably more important than the amount, or severity, of stressful events.

It is possible that some of the social groups that seem to be vulnerable to CFS are particularly prone to stress: doctors for example. The British Medical Association have recently produced a report (British Medical Association 1992) suggesting that doctors are prone to stress due to unsocial hours, high responsibility and traumatic incidents. Stress has been widely suggested as a cause of CFS.

The evidence for stress as a factor in CFS is highly circumstantial. The stress argument in CFS is based on assumptions that CFS is the type of illness that can be produced by known results of stress. It is also based on the assumption that groups vulnerable to CFS have higher than normal stress put upon them.

### 3.4.2 Locus of control and learned helplessness

Skevington (1983) shows that patients with chronic pain tend to have a belief in lack of internal control which Skevington attributes to learned helplessness. Skevington also suggests that the patient comes to believe no one can help. Langer (1983) argues that there is a direct relationship between extent of coping behaviour and degree of belief in control. Rodin and Langer (1980) looking at chronic illness say that when people are experiencing a traumatic event they typically perceive it as time to give up what control they have and their locus of control changes. Persistent pain or illness without power to relieve it could lead one to believe one is not in control of that side of one's life. It may be that CFS patients have a vulnerability to illness because of the direction of their beliefs about control in their lives. Alternatively, or in addition, they may come to a state of learned helplessness or more beliefs about externality of control in their lives due to the illness. In this study locus of control is measured to see if CFS patients show signs of high externality of control.

## 3.5 Neurology of CFS

### 3.5.1 Neurological abnormalities

Evoked potential abnormalities in CFS patients

Prasher, Smith and Findlay (1990) examined cognitive event potentials in ME. They use criteria of fatigue, myalgia, poor concentration and memory with preceding viral illness over 6 months before testing (these criteria exclude non-post-viral patients). They find that in ME patients the event potential P3 is absent or significantly delayed in 52% of patients. The amplitude of P3 provides an indication of attentional capacity devoted to the task and its latency provides a measure of the speed of target detection. They conclude that the results suggest two subgroups, one with attentional deficits and the other with slower speed of information processing. They find this result consistent with complaints of memory and concentration but not with depression, since P3 latency, they state, is not found in depressed patients.

Sleep abnormalities in CFS patients

Whelton, Salit, and Moldofsky (1992) show, with a small number of CFS patients, a high incidence of sleep apnoea and more alpha EEG activity during NREM sleep. They also point to the similarities in patients with cancer, where interleukin2 and lymphocyte activated killer cells produce sleep disturbance.

Abnormality in CFS patients of pituitary/hypothalamic function.

Demitrack (Demitrack 1991) tests 40 CFS patients (according to CDC criteria) and shows that, compared to controls, CFS have a significant reduction in basal total cortisol. This study uses recognised criteria and suitable controls for comparison. He hypothesises that this and other abnormalities related to the pituitary/adrenal axis suggest a mild hypocortisolism as a result of a defect in the hypothalamus.

Vision

Potazanich and Kozol (1992) show high symptom reporting of ocular problems with little objective evidence.

EEG abnormalities in CFS patients.

Pampiglione (1978) examines EEG's in 46 patients with a symptomatology of ME and find abnormalities - excess of intermediate slow activity in particular areas (no controls were used).

SPECT Scans and decreased blood flow in CFS patients

Mena (Mena and Villanueva-Meyer 1992) uses SPECT scans to examine blood flow to the brain and discovers areas of decreased blood flow particularly in the temporal lobes. She considers the decrease significant but not irreversible. These kind of blood flow changes are also found in migraine and depressed patients (Dolan et al. 1991), as well as subcortical diseases such as Parkinson's disease and Huntingdon's disease (Abbey and Garfinkel 1991; Cunnings 1992), so again the significance of such findings in CFS patients is not known. Mena and Villanueva-Meyer (1992) find 71% of CFS patients scans show unilateral or bilateral hypofusion in the temporal lobes. Individual scans (Hyde, Biddle and McNamara 1992 and Bastien 1992) show the areas most affected are sub-cortical, left parietal lobe, right medial lobe of the cerebellum and temporal lobe. SPECT scans show decreased brain perfusion up to 24 hours after exercise or sleep deprivation in CFS patients. Goldstein (1992) comments on the results of Mena's work and concludes that CFS patients have a lower metabolic rate in the hippocampus and amygdala, as well as the caudate nucleus, the premotor cortex and the anterior cerebellum. Early reports of similar results from the Middlesex Hospital, London conducted by Honorary Consultant Physician Dr Durval Costa (MacIntyre 1992) with 500 patients suggests that these results are found in a large percentage of CFS patients and therefore may prove an important finding in CFS.

MRI scans on CFS patients

Biddle (Hyde, Biddle and McNamara 1992) reports on MRI scans in California. Two groups, 142 CFS and controls, were scanned. In 79% of CFS patients areas of increased signal intensity occurred; which was significantly different from controls (only 21% of which showed abnormality). Biddle (Hyde, Biddle and McNamara 1992) suggests these unidentified bright objects (UBOs, as they are now known) are perivascular spaces caused by lymphocytes congregating in the perivascular spaces of the brain causing more frequent occurrence of the spaces in CFS patients.

McNamara (1992) examining patients from the Lake Tao area observes that UBO's are most often found in the white matter, subcortical, frontal and parietal areas of the brain. McNamara finds 36 out of 60 patients abnormal on MRI and he suggests that the UBO's represent focal oedema probably in the perivascular (Virchow-Robin) spaces. The meaning and importance of this finding is not clear, indeed it may be that this finding is not very abnormal.

### 3.5.2 Theories of neurological abnormality in CFS patients

The limbic system and the hypothalamus

Goldstein (1992) discusses the possible role of the limbic system in CFS. The limbic system has an important role in the regulating of the autonomic nervous system. The hypothalamus co-ordinates electrolyte balance, basal temperature, metabolic rate, autonomic tone, sexual libido, circadian rhythms and immunoregulation. From evidence in temporal lobe epilepsy he suggests that there is evidence of a fatigue receptor in the medial temporal lobe that could be affected in CFS and that vertigo, often a feature of CFS, can be produced by stimulation of the temporal lobe. The limbic and paralimbic areas have higher levels of endogenous opioid activity and receptor activation in the hippocampus could account for weight gain and intolerance of alcohol.

Goldstein says that lesions in the paralimbic structures produce less profound memory and learning impairment and they are less involved in the channelling of drive and affect than in the limbic system itself. Goldstein relates problems in the limbic system to immunisations and/or altered neuronal or monoamine metabolism. He hypothesises that CFS is a limbic encephalopathy in the dysregulated neuroimmune network. Arnason (1991) also points out that the pituitary can affect the immune system.

Smith (1991) concludes that the kind of difficulties he finds - slowed reaction time, problems with visual illusion and Stroop effects - might be indicative of problems in the hypothalmus produced by viral effects on the immune system.

### 3.5.3 Abnormality of Arousal in CFS patients.

Grafman et al. (1991) write that fatigue can be 'viewed as a result of decreased arousal'. In CFS both decreased and increased physical arousal may occur. The possibility that CFS patients may be physiologically aroused inappropriately is supported by the presence of symptoms related to inappropriate overarousal to physical stimuli. CFS patients show hypersensitivity to light and sound and temperature. They sweat profusely at times, they "go white" and produce a heightened blush type response. They also complain of symptoms that relate to sleep problems such as vivid coloured dreams. It is possible that fatigue could be related to underarousal in the day and overarousal at night, whether depression and anxiety would be caused by over and under arousal or cause such disturbance, require careful consideration. The physiology of arousal is complex: damage in a number of areas or neurotransmitter abnormalities could cause such problems.

### 3.5.4 Claims of extensive neurological disturbance

Observations of general neurology problems in CFS have been very varied and comprehensive. The following lists are made from two recent reports (items in the lists

which are supported from other papers are marked with a *). Richardson (1992) reports the following symptoms in CFS without quoting evidence: bladder dysfunction misdiagnosed as cystitis or urinary tract infection in CFS, may be due to hypothalamic disorder; akinetic lapses, patients are aware of surroundings but are unable to respond or move; seizure activity; absence spells are often noticed by the family; grand mal or Jacksonian type seizures do occur but are likely to remit; Cogwheel rigidity; modified Romberg Abnormality*; failure to focus due to jitter like movement in the eye nystagmus*; pain behind the ear, with high sounds, which may be of hypothalamic origin; facial pallor; abnormal amounts of thyroid antibodies.

Hyde and Jain (1992(b)) report in a review paper: anterior horn cell injury-injury in the spinal cord; central endocrine system - fluid balance, thyroid balance*, temperature regulation and sexual dysfunction; natural killer cell dysfunction*; blood pressure regulation dysfunction; acquired cognitive dysfunctions, drop in IQ level dysfunction in simultaneous processing, distraction, not able to concentrate, dysphasia, reading problems*, visual comprehension and discrimination dysfunction, facial agnosia, discalculia, abstract reasoning dysfunction, volition dysfunction, proprioceptive dysfunction; sleep abnormalities* and colour dreams; sleep apnoea and hypothermia; sensory dysfunction; apraxia; auditory dysfunction; photophobia*; latency of accommodation*; failure of the eyes to track together, tunnel vision, night vision loss, colour vision loss, palpebral oedema; writing problems, distance and facial dysfunction, jay walking, depth of field dysfunction.

The reason for reporting these two papers is to indicate the range of neurological type symptoms that have been said to exist in CFS but for which supporting evidence is not necessarily given. The investigation of these supposed features of CFS has occurred in those that have a star* and are discussed throughout this and the following sections. Parish (1978(a)) mentions some of the symptoms such as photophobia, in writing about the Royal Free. Ramsay (1981) writes about dysphasic misfinding of words and colour dreams. Many of these symptoms could relate to hypothalamic dysfunction. However,

if most patients exhibited a number of these neurological symptoms over a long period one would expect more evidence of these symptoms would exist. These severe neurological-type symptoms are not evident in all CFS patients. It is likely that they are particular to certain groups of patients, e.g. Bastien's patients in Nevada or the patients in the Royal Free 1955 epidemic.

## 3.6 Memory and Psychomotor Testing

### 3.6.1. Cognitive Problems in CFS/ME

CFS from the neuropsychological viewpoint raises a number of issues. Patients' complaints include: depression, anxiety, memory loss, loss of concentration, word finding and particularly naming difficulties, and others (these appear as symptoms in the literature, Archer 1987). Physicians report neurological symptoms (Parish 1978(a)) which for a few patients are similar to, and as severe as, those found in encephalitis. Peterson, Schenck and Sherman (1991) show a large percentage of subjects with neuropsychological complaints, from mild to severe, from a more recent outbreak (see Appendix 1 Table 11). Parish (1978(a)) reports 60% mentioning neurological findings with 20% showing objective findings in the Dalston epidemic; but suggests that for the Royal Free epidemic, 50% had neurological symptoms. Crowley, Nelson and Stovin (1957) show a third of patients with moderate or severe objective neurological signs (see Appendix 1 Table 7). On the other hand, in most cases patients' objective difficulties do not seem to match patients' reports (as mentioned previously), and where patients have been tested individually for memory problems etc. recognisable deficits have not often been recorded (Parish 1978(a)).

### 3.6.2 Recent findings testing memory and psychomotor skills in CFS

Studies on memory and cognition in CFS are of recent origin and are still scarce. Smith (Smith 1991) compares cognition in CFS patients with the effects on cognition of the

early stage of a cold or injected interferon. Smith's study is done with volunteers chosen by their symptoms and a positive VP1 result, obtained through the ME Association, but Smith does not give details. This group, no doubt, allows him a large body of patients but may be rather unsatisfactory in terms of being representative of the whole CFS population and the criteria for diagnosis that are being used are not clear. Smith finds differences with controls on reaction time, Stroop and visual illusion (Smith 1991). Smith records a pattern of deficit in reaction time with CFS patients who he classes as severely ill according to level of EBV antibodies and positive VP1. Severely ill CFS patients scored an average of 409 milliseconds (number=18), mildly ill CFS patients 355 milliseconds and Normals 253 milliseconds (number=9) on a single choice reaction-time task. The difference between severely ill and mildly ill CFS patients in Smith's study might also be seen with the same patients at different testings in a longitudinal study.

Smith reports that CFS patients are more susceptible to visual illusion and they are slower and less accurate on visual search tasks. Smith shows a difference in CFS patients' memory in the primacy effect on verbal learning. CFS patients score well on this test by giving a high number of false alarms which Smith claims to be indicative of possible mamilliary body damage. On Stroop CFS are slower in the colour naming condition. Smith puts this down to them being more distracted by alternative stimuli. Smith's results show strong reaction time differences and problems with visual effects, and may indicate possible slight memory problems. He claims that these are results you would not expect with depressed patients; however his CFS subjects scored much higher on depression, anxiety and somatic symptoms on the Middlesex Health Questionnaire (MHQ). He suggests that longitudinal studies would be valuable to show whether CFS patients improve with recovery.

Kilfedder (1988) found a mismatch between reporting of, and objective testing of, cognitive symptoms, but increased ataxia, slower reaction time and increased anxiety and depression in CFS patients. The subject numbers are small partly because the CFS group was divided into those with or without coxsackie titres but it is reported that CFS

patients do less well against normals on Rey Figure immediate recall.

Bastien (1992) examines 81 patients from the Nevada, Incline Village epidemic; they meet the CDC criteria for CFS. Bastien finds significant impairments on a number of tests. The term impairment implies below normal functioning, i.e. below norms for the particular tests; Bastien states that she is using Halstead-Reitan cut off to judge impairment cut off levels; control data are not used. Bastien reports deficits on Wechsler Memory Verbal Recall for 85% of CFS subjects, for 80% on Delayed Verbal Recall and 54% for the category part of the FAS word fluency test. Bastien also find impairment in finger tapping with the dominant hand, and tactual performance with both hands. Most spectacular of all are her pictures showing gross immaturity in the Draw-a-Person Test drawn by CFS patients. This test can be used to show emotional indicators but in this case she suggests it is more valid as an organic indicator. Literature surveys of this area show no confirmatory evidence of this rather unusual finding.

Bastien seems to have found a much more impaired group than previous evidence suggests. This suggests Bastien's patients may be different from the CFS population in general or Bastien's criteria for deficit are less rigorous; it is a pity that Bastien does not use control data to show that her patients are impaired in relation to a normal group. From Bastien's results she suggests that there are abnormalities in the brain functioning in the left temporal lobe (WMS deficits) and parietal lobe (Tactual performance) and left frontal lobe motor strip (Finger Tapping). She suggests that the impairment shows a multi focal organic brain syndrome and that the most impaired areas are left temporal, right parietal and left frontal lobes.

Lane (1992) reports results from routine examination of a CFS patient group. It is not clear by which criteria this group are diagnosed, although he gives a very general description: fatigue, malaise, weakness, myalgia, exercise problem and other symptoms as a description at the beginning of the paper. He finds no significant decline from general estimated pre-morbid IQ capacities. Lane finds 20% of CFS patients performed

badly on visual and verbal memory. But he finds a considerable proportion (50%) who had a discrepancy between verbal and visual memory tasks (verbal memory being worse), on a forced word versus a forced faces test.

No controls are used in Lane's (1992) study. He finds surprisingly few of the CFS patients to be depressed on Beck's scale. Lane does not take the view that these cognitive differences coupled with the neurological abnormalities he finds were necessarily due to CFS damage, but suggests that they resemble the symptoms of hyperventilation.

### 3.6.3 Negative findings of poor cognitive performance in CFS patients

In Altay et al.'s (1990) study there are 21 patients, using defining criteria of fatigue/weakness, a post infectious episode, and an absence of laboratory findings; they have an average age of 36 and education mean of 16.5 years. Tests are WAIS R Similarities, Trails B Similarities, Digit Symbol and Vocabulary Abstraction. The CFS subjects all perform significantly better than controls although 20 out of 21 of subjects felt that they were performing poorly.

The main problem of Altay et al.'s study is that they do not control for IQ; Altay states that his post infectious neuromyasthenia patients have higher educational and achievement levels than controls. Altay also does not state how ill patients were during the study. It would have been an advantage to know how they would test against themselves when well. Patients' perceptions of not performing well are attributed by Altay et al. (1990) to psychological problems; it may however relate to effort and speed, not quality of performance. The person may be performing adequately but below his/her is normal.

### 3.6.4 Summary

The evidence of cognitive deficits so far suggests reaction time slowing in performance and verbal and visual memory problems. However, considerable difference of opinion remains about whether CFS patients do have memory and psychomotor problems. This is because differences between groups in research in the area have not been found in some studies, or have only been very small, or they have been studies where CFS is poorly defined or a control group has not been used.

## 4. Summary of the literature and conclusions for design of further research

### 4.1 Summary of symptoms in diagram form

Symptomatology of CFS and Etiology

As indicated in the literature survey, the symptoms of CFS patients can be differently attributed to an organic or psychological model. Figures 2 and 3 following, show diagrams mapping possible symptom causes; they sum up the more important causes of symptoms according to the two opposing models. Arrows pointing into the "Symptoms" box indicate that these influences cause or exacerbate CFS symptoms. Arrows pointing both ways suggest positive feedback loops; for example, depression causes symptoms (e.g. psychomotor slowing), and the symptoms of CFS cause depression to increase. Some pathways to the symptoms are thus also indicated, for example the subject's type of work causing stress, stress causing normal fatigue and the fatigue developing into symptoms. These diagrams show how each model could work according to either perspective; these diagrams have many possible elaborations, however what is important is to see that both theoretical points of view can account for CFS symptoms. One of the problems with models of CFS is that the possible relationships between symptoms are so numerous. Figure 2 for example has so many possible variations that one can end up with a model so complicated and convoluted as to be of no value.

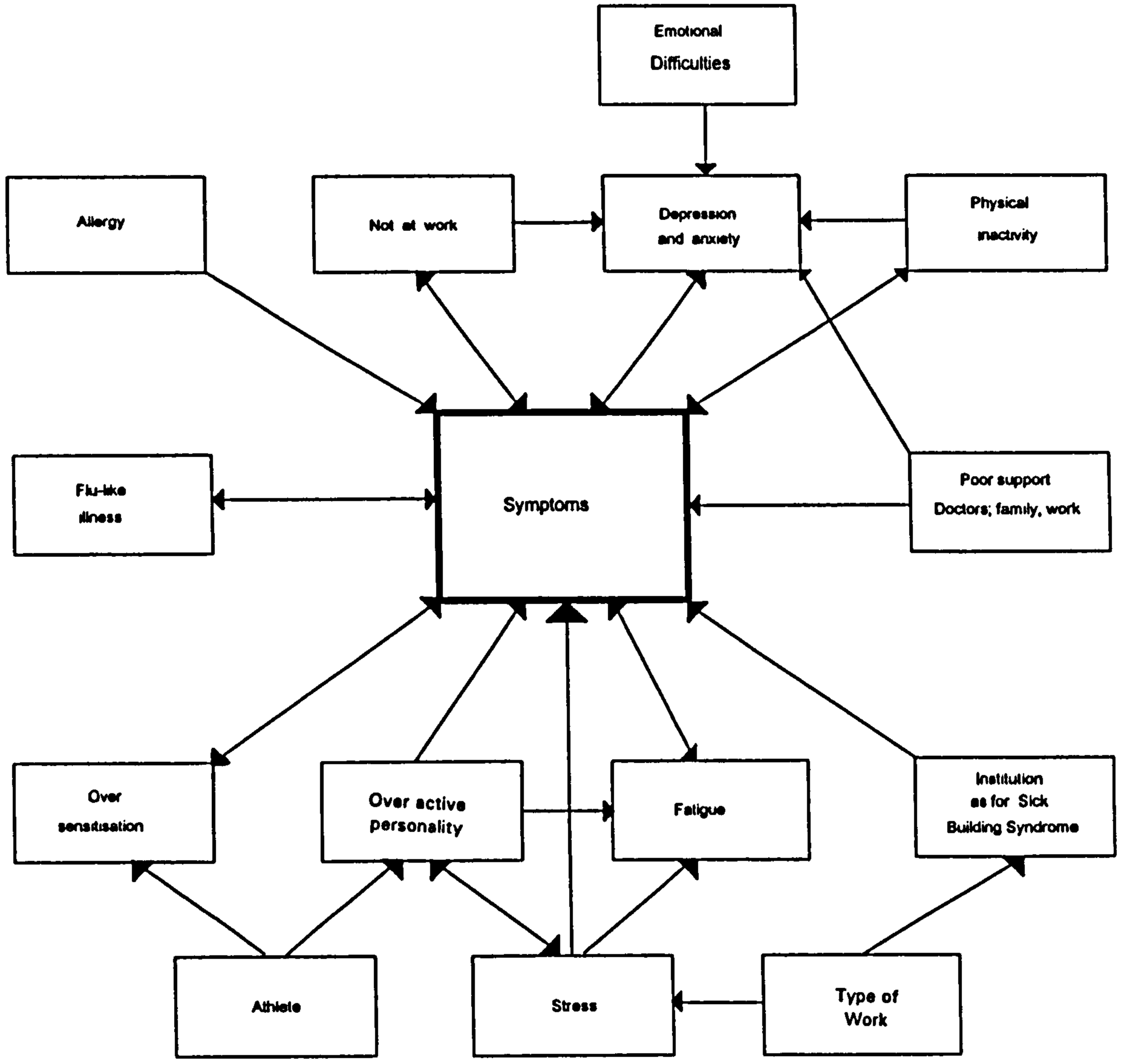



**Figure 2: Possible causes of symptoms (a): not particular to CFS**

✳ Damage from trigger illness / other unknown causes

1,2 show related concepts

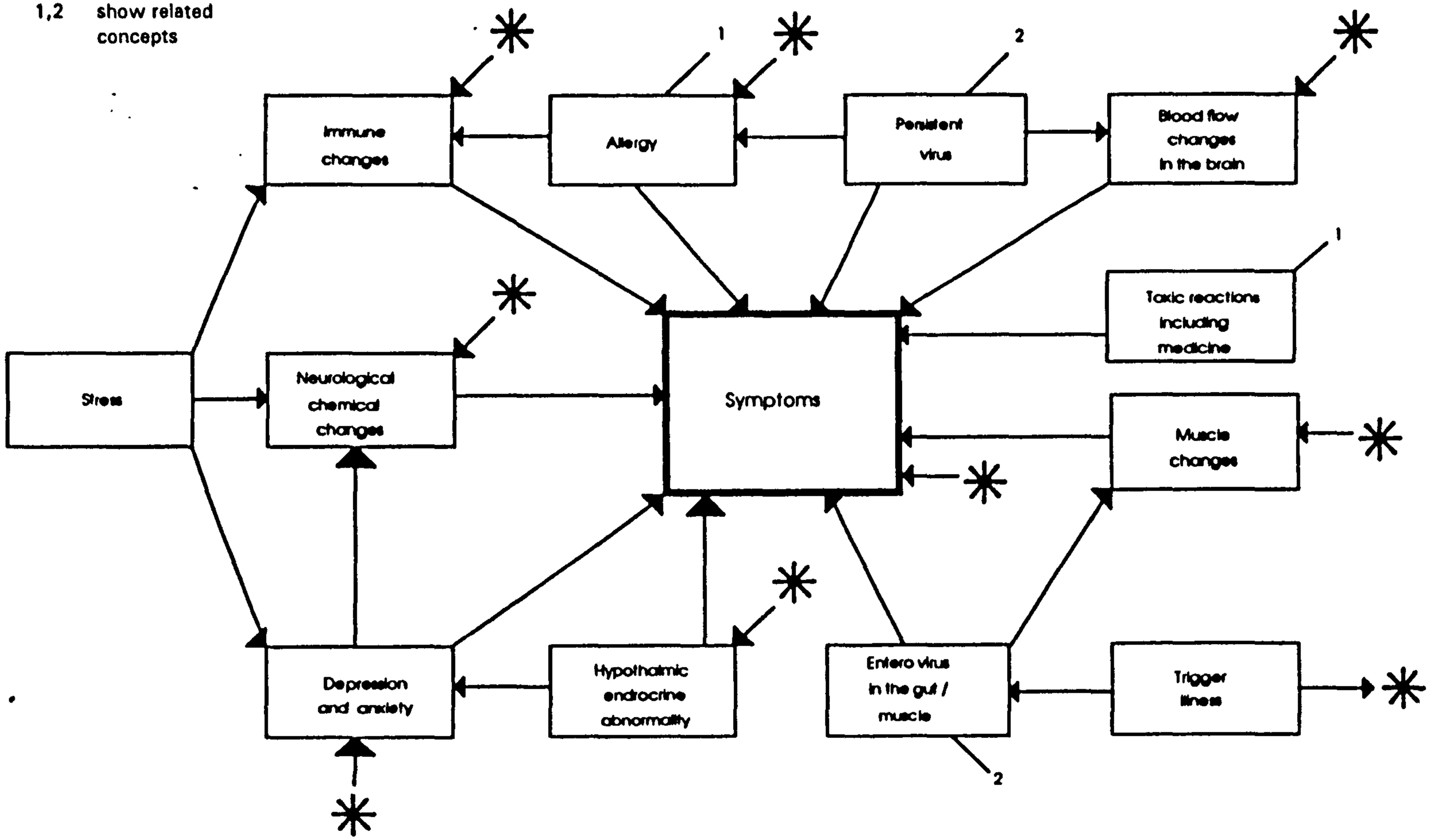



**Figure 3: Possible causes of symptoms in an organic model for a CFS entity**

## 4.2 Summary of points made in the literature survey

Part one of the literature survey.

1. The prevalence of CFS in the population is high.
2. The symptoms of CFS are of a common nature.
3. Many studies of abnormality in CFS have used small groups and lacked control groups, although some evidence suggest organic damage in CFS.
4. Clear criteria for CFS diagnosis is necessary; however, many studies of CFS have lacked a proper definition of CFS.
5. Vulnerability to CFS is associated with demographic and geographic variables.
6. CFS patients recover from CFS spontaneously, in most cases.

Part two of the literature survey.

1. There are two main parts of the literature; early epidemic ME and later sporadic CFS.
2. There is disagreement as to whether these two parts of the literature are about the same illness.

Part three of the literature survey.

1. Complaints about cognition in CFS have not been matched by corresponding deficits.
2. Depression scores are high in CFS patients.
3. There are great difficulties in assessing whether depression in CFS is due to illness or illness is caused by depression.
4. Other psychiatric differences in CFS patients may include hysteria, somatisation, high anxiety and high psychiatric history prior to illness.
5. Results from tests on memory suggest that there may be a problem with visual and verbal memory.
6. Results from tests of psychomotor skills suggests CFS patients are slower on reaction time tasks.

7. CFS patients have also been reported by single studies to be susceptible to visual illusion and to have problems drawing people.
8. Bastien's study suggests CFS patients' IQ level is reduced.
9. Tests of cognition with controls have been rare.
10. Studies of cognition and psychomotor skills are inconsistent, some studies showing CFS patients as better on tests than controls.

Neurological studies suggest:

11. that CFS patients may have a problem with hypothalamic - pituitary function;
12. that CFS patients may have decreased blood flow to some areas of the brain;
13. that CFS patients have delayed P.3 evoked potentials;
14. that CFS patients may have sleep abnormalities.

**4.3 Further research needs in the neuropsychology of CFS.**

The literature survey shows the need for studies where CFS is clearly defined and suitable controls are used. In the area of neuropsychology the research is patchy. A number of studies have proved that CFS populations have high depression levels but research is still needed to confirm the existence and extent of other neuropsychological problems in CFS patients. Research into the neuropsychology of CFS has had methodological and definition problems. The literature also indicates the need to take into account the following:

1. recovery in CFS;
2. depression in CFS;
3. possible IQ changes in CFS.

In addition the literature shows that one needs to design the study with controls; preferably a normal group and a chronically ill or depressed group.

The following study, therefore, was designed to cover all the points in 1-3 above. Subjects were CFS patients, Crohns/colitis patients and normal controls. The groups

were to be matched on the NART (very stable IQ test), by Age and by Sex. The groups were to be seen 4-6 monthly and tested on a neuropsychological test battery. This battery was to include those areas indicated as being most likely to be affected by CFS i.e. memory both verbal and visual, drawing and spatial memory, reaction time, speech and word fluency and other tests to cover common areas of neuropsychological difficulty.

The studies mentioned in the neuropsychological section were not all available when the study was designed, so evidence for decline in IQ, and most of the evidence of poor cognitive performance, were not available at that time. Nevertheless from the evidence of patient complaints and other information in the literature these were taken into account.

**4.4 Confirmation in later literature of the correctness of the design of the proposed study.**

After the study was designed in December 1988, a number of articles came out that recommended that similar design and methodology in future studies to that we had used.

Grafman (Grafman, Johnson and Scheffers 1991) remarks that a number of reports in CFS show a mild drop in performance, but that none include a formal neuropsychological evaluation of patients with controls. Since then Smith (1991) neuropsychological assessment has been published (in 1988 Kilfedder's thesis had become available for study, although unpublished), but Grafman's remark again shows that this study anticipated an area where the lack of information was already being noted.

Stricklin (1991) regrets not using chronic controls in his study in 1991 although chronic controls had only just begun to be used at that time; Wessely (1989) uses patients with muscular illness and Katon et al.'s Rheumatoid arthritis patients in 1991 (an M.Sc. student at Glasgow also chose Crohns patients for a comparison of mood and CFS

during our study). Sharpe et al. (1991) advocates multiple control groups to compare with CFS in order to avoid 'pitfalls' created by sole use of normal controls. This study is rare in having used two control groups.

In doing a longitudinal study this work forestalls Sharpe et al. (1991) who suggests that longitudinal studies should be used in CFS to establish temporal sequence. Wessely goes further: "perhaps the most valuable, albeit scarce [data] (on both the risk factors and prognosis of CFS), comes from longitudinal studies of the outcome of defined infections" (Wessely 1992).

In 1991, after our study was started, Becker (1991) brought out a paper on investigating CFS. He produces a similar test battery for looking at IQ, memory (verbal and visual recognition and recall), attention (including reaction time and visual attention), Word fluency, and depression, anxiety and fatigue. This again is a vindication of the method and tests used in the study reported in this thesis.

Apart from these specific verifications, that show this study was methodologically wise and necessary, other aspects of this study now seem more justified rather than less justified. When work was started on this research the central importance of 'depression' was not so evident. Taerke's (Taerke et al. 1987) work had been published but Katon et al. (1991), Kruesi et al. (1989) and Wessely (1990(b)) had not. There is now no doubt that one has to consider depression in any study of cognition in CFS patients, but at the time of the study the evidence was less strong. Because depression has been looked at in the study this work is much more valuable than it would otherwise have been.

At this stage, too, work to pin down diagnosis and to define the criteria used had just begun; if the research had been done later Sharpe's criteria might have been used (Sharpe et al. 1991) but at the time it wasn't available. In basing the criteria of the research on Holmes the study utilised the now most widely adopted criteria, even though it was to be simplified for use at Rucchill hospital.

The CES-D scale has also become quite popular (e.g. Hurwicz and Berkanovic 1993, Neugebauer et al. 1992) though it was less widely used prior to 1988, except for epidemiological studies.

In short, this study's design fitted a gap both methodologically and in knowledge which became evident in the literature published during its execution.

### 4.5 Aims of proposed study

Previous studies of psychological aspects in CFS have tended to concentrate on the affective aspects of the illness (e.g. Taerke et al. 1987; David et al. 1988). CFS patients complain of many neuropsychological problems, by far the most common being difficulties with memory, concentration and word fluency (Archer 1987). Other neuro-psychological complaints include difficulties with speech, photophobia, loss of sensation in parts of the body, mood and personality changes. Appendix 1 Table 11 shows the percentage of patients with each kind of difficulty in a study by Petersen et al. (1991). While those with acute encephalitic symptoms - i.e. a combination of more severe symptoms such as stiff neck, photophobia, delirium, severe headache or noticeable difficulties with movement or speech - should have had some kind of neuropsychological assessment, those with milder symptoms may not have been tested, or not in such a way as to pick up a small decrement in performance. This study is a formal assessment with controls (two groups); it also looks at changing performance over time on neuropsychological tests relevant to problems recorded in CFS.

# CHAPTER 3. METHOD

## 1 Aims

### 1.1 Introduction

This study was of CFS patients compared with a chronically ill group of patients and normal controls. It examined changing cognitive performance and psychological profile during the illness.

### 1.2 Objectives

The objectives of the project were:-

1) to test neuropsychological performance in CFS patients to assess whether their performance is worse on some tasks than controls;
2) to monitor neuropsychological performance in CFS patients, while they are recovering from CFS, and compare them to controls over a similar period; the aim is to see if CFS patients improve on neuropsychological performance more than controls;
3) to compare depression and anxiety levels in CFS patients with another chronic patient group and normal controls; to assess whether differences in performance can be accounted for by anxiety or depression;
4) to compare CFS, chronic patients and normal subjects on psychological, demographic, health and activity variables.

### 1.3 Null hypotheses

In order to test these aims a number of null hypotheses were used

1. Average performance of CFS patients, chronic controls and normal controls on items from a neuropsychological test battery are the same.
2. CFS patients show the same improvement as controls on items of the test battery

when it is repeated.

3. Average scores of CFS patients, chronic controls and normal controls on depression or anxiety questionnaires are the same.
4. Average performance of CFS patients is the same as that of normal controls on items from a neuropsychological test battery after adjusting for differences in depression score.
5. CFS patients do not differ significantly from controls on number of major life events or locus of control questionnaires.
6. CFS patients do not differ significantly from controls on demographic, health or activity data.

The use of tests to make multiple comparisons of means (as in 1. and 3.) is discussed further in Section 9.1.

## 2. Subjects

Three groups of subjects were used. The CFS patient group, which were the experimental group, and two control groups. The first control group was taken from the normal population. The second control group was used to control for the effects of chronic illness, particularly depression. Both control groups were matched to the CFS group for IQ and age.

### 2.1 CFS subjects

CFS subjects were 45 patients diagnosed as having Chronic Fatigue Syndrome and not excluded from the study by criteria shown in Table 2. Two other patients filled in general questionnaires but were not available to carry out the cognitive tests.

The criteria for selection of CFS patients were developed by Dr I. W. Pinkerton (Consultant Physician and Head of the Department of Infectious Diseases, Ruchill Hospital Glasgow) and the experimenter and agreed by all consultants referring patients.

**Table 2: Chronic Fatigue Syndrome: diagnostic criteria**

The diagnosis of Chronic Fatigue Syndrome is based on clinical judgement and depends on the following criteria:-

Major Criteria (All cases)

1) Persistent but fluctuating fatigue over a period of 3 months - with or without initial febrile illness.

2) Muscle fatiguability (without demonstrable weakness on clinical examination) -with or without muscle pain.

These otherwise unexplained on full clinical examination and in the absence of clinical or laboratory evidence of other disease processes as specified below*.

Minor Criteria

It is expected, but not a requirement, that the patient will have several of the following:

1) Muscle pain.

2) Perception of impaired concentration, particularly on reading.

3) Sensitivity to light.

4) Dizziness.

5) Slightly enlarged lymph nodes.

6) Difficulty getting to sleep.

* Patients should be afebrile and have a normal blood count and differential, a normal ESR, no significant weight loss and a normal chest X-ray.

The criteria were based on Holmes et al. (1988) and on early reports of the comments by Ho Yen (1991). The study commenced in early 1989 and, therefore, other criteria were not available for study. The six month period after initial illness used by Holmes et al. (1988) was reduced to 3 months because the patients were to be studied longitudinally. In this way patients with a short history could be studied from the more severe phases of their illness and any patients who were no longer ill at six months could be regarded as not having CFS and could be dropped from the study (most patients came to the study with a longer history and none were ill for less than six months before recovering). Patients were not excluded because of depression from the diagnosis of CFS. However, patients with previous psychiatric history or on antidepressants were not included in the study. This was for two main reasons: 1) they might be expected to perform poorly on the tests because of their mental state or medications and 2) it might be that those with prior psychiatric illness form a different category (Holmes 1990). The CFS subjects were nearly all patients attending Ruchill Hospital. Most of the patients were newly diagnosed as having CFS.

Patients who fitted the diagnostic criteria were asked whether they were willing to take part by a consultant general physician in infectious diseases or by letter from the author. These patients were told by the consultant or experimenter and by the letter, that the study in which they were being asked to take part was looking at memory and concentration in CFS patients. Most patients expressed interest according to the ancedotal report but the consultant did not keep a written record of the response rate; all those who were sent to the author except two agreed to take part. This was a methodological weakness; it was requested that the information be kept, but the reporting was outside the author's control, and did not occur. If the patient expressed interest, the initial information was sent or given to the patient by the experimenter. This initial information consisted of a pro-forma letter informing the patient what the research was for and what would happen at the research session; it was sent together with a standard consent form (both shown in Appendix 2 Item 2a).

Three subjects were diagnosed as having CFS at other hospitals and requested to take part after a radio programme. They were tested at Ruchill Hospital or Stirling University. Patients were not tested until at least 6 weeks after the initial onset of the illness according to their clinical history.

**2.2 Control groups: normal subjects**

The normal control group consisted of 41 normal controls taken from the St Andrews Ambulance Service.

The choice of control group was arrived at by considering several factors. The control group would need above average IQ (because CFS patients are typically generally higher than average IQ), be predominantly in the age group 18 to 50, and include both sexes. It was preferable not to use medical staff because they would be knowledgeable about illness and would have beliefs and expectations influenced by their work.

St Andrews Ambulance volunteers offered a large pool of potential volunteers. They might be expected to have above average IQ (because they had to do an examination for the course it was expected they would self select themselves as higher than average IQ). They were also interested in medicine and were already volunteers so it was thought likely that they would co-operate. A disadvantage was that being volunteers might mean they were slightly atypical of the general population. However, since the CFS patients also seemed to be people who were very active, enthusiastic and involved in lots of activities before their illness, this made the two groups more alike and therefore increased the likelihood of endorsing the null hypotheses. Both the pre-morbid CFS group and the normal controls seemed more athletic than the general population.

Normal subjects were volunteers from public classes run by the St Andrews Ambulance Brigade. The President of St Andrews Ambulance (Dr Pinkerton) and the experimenter spoke to the class explaining the study and they were given an explanation sheet

(Appendix 2 Item 2b) and an appointment at a time convenient to them. The President explained that CFS/ME was a mysterious disease which had particularly affected Scotland and that the study was to test memory and concentration problems in Chronic Fatigue Syndrome patients with which their results would be compared. The normal controls were required, after studying the explanatory sheet, to fill in a consent form at time of testing. They were seen normally in the evening after work so they were expected to be more tired than if seen in the day. They were (except for two members of this group) seen at St Andrews Ambulance Headquarters in Glasgow.

**2.3 Control groups: Crohns/colitis patients**

This group was chosen for similarity to the CFS group, as follows. It consisted of 28 Crohns or colitis patients. The choice of a medical group which was similar both in terms of length of illness, chronicity and disability was made on advice from consultant physician and head of the Infectious Diseases Department, Dr Pinkerton. Two groups were considered: a rheumatoid arthritis group and a group with chronic bowel disorder. The rheumatoid group were rejected on the grounds that they were too different in age composition, the disease had more disability and it was more progressive.

Of the bowel disorder group, it was decided that Irritable Bowel Syndrome patients should not be included because of the lack of objective diagnostic tests and its high association with psychological factors. It was decided to use patients from the bowel disorder group who had objective signs of bowel disease and two groups were included: those with Crohns disease and those with colitis (chronic inflammatory bowel disease). Approximately 1/3 to 2/3 Crohns to colitis were seen, but they are not very discrete groups in that diagnosis may be switched from colitis to Crohns; illness is normally more severe in Crohns disease. One main difference in the two is that inflammation in the bowel is generally more widespread in Crohns and harder to cure. The advantage of having this combination of Crohns/colitis therefore was that it was similar to the makeup of the CFS group, which comprised of about a third of patients who had been patients

longer and been more severely affected by CFS than the rest of the group.

Patients in this group all came from Consultants in Gastroenterology from Stobhill Hospital. All but four were seen by the Senior Consultant and then by the author at the Consultant's outpatient clinic, the others were contacted by post or while they were in-patients. The consultant told his patients that the study being carried out was looking at memory and concentration in CFS and bowel disorder patients; they were given the explanation sheet shown in Appendix 2 Item 2c.

**2.4 Exclusion criteria and non-selection of subjects**

Patients are generally not considered suitable for testing on cognitive data (Gillham et al. 1988; Dikmen et al. 1986; Wilson et al. 1988; Wechsler 1955; Wittenborn 1990; Lezak 1983) if

- they were currently taking tranquilisers or anticonvulsants;
- they had a history of psychiatric disorder;
- they had received hospital treatment for head injury;
- they had a history of drug or alcohol abuse;
- they were under 16 or over 60.

Subjects who had one or more of these were excluded from the main study (cognitive testing and CES-D and State Trait anxiety tests), although questionnaire data was collected from them. Subjects who came into these categories during testing were excluded from the point at which they came into the excluded category, e.g. started taking tranquilisers or antidepressants.

Exclusion criteria in detail

1. Patients were excluded if they were currently (i.e. taken within the last two weeks) on sedatives, tricyclics or other antidepressant. They were excluded if they were taking anticonvulsants, i.e. Sodium Valporate, Carbamazepine, Phenytoin, or any other of this type of drugs or combination of them.

2. If the subject had had treatment from a psychiatrist as recorded in their notes and

checked with the patient (this would not include a referral where no treatment was thought appropriate), or if they had been on long term (i.e. over a year) antidepressants or tranquilisers for psychiatric symptoms, they were considered to have a psychiatric history (only one person came in the second category, and he was taking a cocktail of antidepressants and tranquilisers, and had done so over a number of years, without psychiatric referral). The exception to this was if these drugs were given for CFS or just prior to a diagnosis of CFS, because in that case they might be indicative only of CFS symptomatology.

3. Head Injury. Subjects were excluded if they had been hospitalised over-night for head injury. A superficial wound was not included but substantial head injury, e.g. a fractured skull, counted, however long since it took place. It was recognised that some hospitals keep people in for observation more readily than others, but it was considered that it is unusual to do so unless potential damage is expected.

4. Drug and alcohol abuse. Patients were excluded if they had received treatment for addiction to drugs or alcohol, or these were recorded as a problem in their medical notes, or if they admitted to a serious problem with alcohol or to taking drugs on a regular basis or recently. Scores were taken of alcohol consumption disclosed per week, and if these amounts were excessive the client could be challenged about whether they had an alcohol problem.

5. Age criteria referred to age at first referral.

Exclusion criteria applied affected the following.

- The consultant indicated to the experimenter why he had decided a patient was unsuitable for testing because of the above criteria; the most common reason for non-inclusion was psychiatric history or being on antidepressants. This is not surprising, since some GP's treat CFS with antidepressants. Since patients were rejected by consultants, and the consultants did not keep numbers, the exact numbers are not known. Of patients who had had CFS for over 3 years, a large number seemed to come into this category; an estimate of this from case notes of excluded patients would be up to 50%. New patients were rejected on these grounds much less often;

about twice as often as exclusions for other reasons. A much smaller proportion was excluded on the grounds of age or prior head injury (it is estimated this group was less than 5% of potential patients).

- Normal subjects were informed of exclusion criteria before they volunteered to take part. Three people indicated that the exclusions applied to them but others may have decided not to volunteer because the exclusion criteria applied to them, without indicating so.
- Seven Crohns/colitis patients were excluded by the experimenter; the numbers are not known of how many exclusions were made at an earlier stage.

(Appendix 3 Table 3 gives the breakdown of these figures).

Non-selection for other reasons.

Appendix 3 Table 3 also details the reasons why some of the selected patients never entered into the study, and why some non-excluded potential subjects were not entered into the study. This includes consultants' decisions and numbers of patients who did not turn up. The main effect on the study was that of a gastroenterology consultant not sending patients who were slightly emotional or upset when they saw him. This was often because their condition had deteriorated or they had been told that they needed an operation or to go into hospital. This may have resulted in the reduction of the numbers of Crohns/colitis patients with minor depression and thereby increased the difference on mood between CFS and Crohns/colitis patients as discussed later. One normal control and one CFS patient were in mid pregnancy during first testing and completed after the babies were born.

**3. Ethical considerations**

The research was approved by the Stobhill and Ruchill Ethics Committee. Patients were seen by the investigator, consultant or G.P. initially and asked if they would be willing to take part in the study. They received a printed explanation of the study prior to giving their consent (Appendix 2 Item 2a shows the explanation for CFS patients). The research

at all times conformed to the British Psychological Society ethical guidelines.

All subjects were given a consent form which was filled in after they had been given the written statement (describing the test session) and before the test session. When first meeting the subject, general details were taken (name, address etc) and, if time allowed, the general questionnaire (see section 5.3.8 and Appendix 2 Item 1) was given and the subject given the MHQ and Health Locus of Control (HLOC) questionnaires to do at home.

All subjects were free to withdraw from the study at any time. Subjects who volunteered to be reassessed were retested up to three times. Subjects could be withdrawn from the study if they became severly unwell during a session. No one was withdrawn for this reason but the two subjects who had absences during reaction time testing were given neurological examination before continuing and were retested after a longer than normal interval. Care was taken that testing would not interfere with the recovery of patients. It had been thought (and a couple of patients maintained this) that testing might exacerbate the condition by tiring the patient; therefore it was a principle of the study that if testing was found to be detremental to the patient in the longer term (i.e. not just in the next couple of days) testing would be terminated. It was not found that this occurred; patients were of course free to withdraw if they wished. If patients seemed particularly ill at time of testing this could be reviewed with the physician; however at most sessions the subject saw the consultants around the time of testing.

## 4 Independent variables

### 4.1 Group factors

The object of this study is to compare the three groups to see if there are differences due to CFS. Other factors may account for these differences and these have to be taken into account.

### 4.1.1 Crohns/colitis and effects on neuropsychological testing

The Crohns/colitis group have been chosen as representing a chronically ill group. It is possible that this group may experience loss of performance on cognitive tests specifically due to their illness not because of the chronicity of their illness. The differences could occur because of a) the illness itself and b) due to the medicine they are taking.

Examination of the literature in these two areas does not give any evidence of loss of cognitive performance directly on these two counts. Some psychiatric symptoms are associated with diseases of the small intestine, particularly changes of mood and personality (Cooke 1978). There is an association between malabsorption and Crohns/colitis which, as Cooke (1978) shows, may affect cognitive performance. It is possible, therefore, that cognitive performance could be affected by having Crohns/colitis but it is not an established fact and is probably rare in the condition. Therefore the possibility of cognitive performance declining due to Crohns/colitis has been considered in the analysis but decline, if it exists at all, is likely to be small.

In the Literature survey (Section 3.1.4) depression in chronically ill patients has been discussed and this is expected to be seen in Crohns/colitis patients (this expectation may have been false in view of a problem in referral of Crohns/colitis patients as discussed in section 2.4). This can be used to compare depression with cognitive test performance in the two patient groups.

### 4.1.2 Controlling for differences between groups - controlling for IQ

Diagnosed CFS patients are disproportionately middle class and well educated (see "Literature Survey" Section 1.6); they are therefore above average in their IQ and can be expected to have a higher than average pre-morbid cognitive test score. The performance of subjects in general on the Wechsler Memory Scale for example is highly

correlated to educational achievement according to Wechsler (1945). Goldstein (1990(b)) writes "The Wechsler Memory Scale is highly correlated with IQ and so it is not possible to tell whether the scale measures construct memory specifically or intellectual ability" (p.205). In view of this it is essential that IQ is similar in all three subject groups.

In this study an attempt is made to ascertain what performance one might expect from the CFS patients if they were well, i.e. as controls are. It is therefore necessary to take an IQ measure that is not likely to have dropped significantly due to CFS. It is entirely possible that patients are experiencing loss of performance that is not obvious when their scores are taken individually and tested against normal ranges. Normal ranges are usually averages for the whole population; they do not tell us how a person of a particular age and IQ should score except in some detailed studies. Bastien (1992) reports a significant loss of IQ in CFS patients during the illness. Therefore a measure of premorbid ability and a comparable control group is needed for comparison. The original National Adult Reading Scale (NART) test of 50 irregular words was used. It is quick and easy to administer, but more importantly it has been shown to be relatively stable against a fall in IQ level (Nelson and McKenna 1975). Crawford (1992) writes of the NART that it is the 'most widely used measure of pre-morbid intelligence' (p.35) and 'one of the most reliable tests in clinical practise' (p.36).

In addition to using the NART, any change in IQ arising during recovery should be evidenced because the study is longitudinal, with CFS patients being tested as they recover or relapse from the illness.

### 4.1.3 Controlling for differences between groups - subjects pre-morbid functioning

Becker (1991) says "Individual research subjects differ in their pre-morbid level of functioning, with any one individual having strengths and weaknesses in cognitive skills, educational background, history of head injury and problems with substance abuse which may have impact on cognition function and test performance." In order to allow

for these factors not only were CFS subjects tested against controls but also against themselves in terms of improvement; this should nullify the effect of original weaknesses or strengths. We are also controlling for education by use of the NART and we control for head injury and substance abuse by excluding patients with this sort of history (see Method Section 2.4.1).

### 4.1.4 Medication

The Crohns/colitis group were taking medication, mostly sulphasalazine, which is most commonly used in Crohns/colitis. This could not be avoided and may account for the Crohns/colitis group being slightly worse on memory tests. Meningitis has occasionally occurred with sulphasalazine (Alloway and Mitchell 1993). On searching through current literature data bases however, no evidence for direct effects of sulphasalazine on cognitive performance was found.

The CFS patients were not taking antidepressants or other drugs that might be expected to effect cognition, although stemetil or stugeron could cause some drowsiness and in a very extreme case more dramatic side effects. It is extremely unlikely that the 3 patients taking these drugs occasionally could significantly affect overall performance on tests, especially as outliers were excluded (six individual patient test-scores were excluded, as discussed in the Results sections 1.2 and 3.1.3 and Appendix 5). Some CFS patients took medication for symptoms, e.g. anti-inflamatories (although this was rare) and others remedies such as evening primrose oil. A full list of drugs for each group is shown in Appendix 3 Table 4.

## 4.2 The profile of the groups

This section examines characteristics of the populations. The first sub-section describes demographic variables. The following two sub-sections cover general illness variables that will enable comparison of this CFS group with those used in other research.

### 4.2.1 Demographic variables

An Analysis of Variance (ANOVA) followed by a Scheffe test was used to established that there were no significant differences between the means of the groups, on NART, age, alcohol consumption or the number of children of subjects. These variables were chosen to make sure that one group were not different in a way that would make them different apart from their health status, e.g. likely to be stressed (young children, marital status, demographic variables), do more physical activity (less family commitment), or be able to do the tests better (IQ and alchohol consumption). Since stress levels (see Section 3.4) have been suggested as a cause of CFS it was important to ascertain that CFS patients were not different in terms of their family situations. Sex and marital status were found to be similarly distributed on a chi-square test of the group distributions. Details are shown in Table 3. (Not all subjects were willing to give their age and marital status.)

Sex

The male/female ratio was 1:2.06 for the CFS group, 1:1.70 for the Crohns/colitis group and 1:3.56 for the normal controls.

Age and IQ

The distributions of age and IQ (according to NART) for each group is given in Appendix 3 Tables 2A and 2B. Age is not significantly different on the mean of groups, but when age distribution is displayed one can observe that the Crohns/colitis group have less in the 16-25 age group and a high population in the 30-40 age group; however the profile is more similar to that of CFS subjects than it would have been with other chronically ill groups suggested such as rheumatoid arthritis patients. The IQ distributions are not significantly different, but the CFS group has slightly higher percentages in the higher IQ groups.

Table 3 Demographic data: differences between groups.

This Table compares the demographic variables for the three groups, CFS, normals and Crohns/colitis patients. Four variables were compared with an ANOVA followed by a Scheffe test. Two further variables were compared with a Chi-squared test.

| | Variable | <------ GROUP ------> CFS | Normal | Chronic | F-ratio | Significance differences at 5% level |
|---|---|---|---|---|---|---|
| (i) | NART (errors) predicted verbal IQ | 16.60 (113) | 20.03 (111) | 19.91 (111) | F(2,97)=1.88 | Not sig. |
| (ii) | Age (years) | 34.73 | 32.71 | 35.56 | F(2,109)=0.55 | Not sig. |
| (iii) | Alcohol consumption (units/week) | 3.16 | 4.18 | 3.23 | F(2,72)=0.36 | Not sig. |
| (iv) | Number of children | 0.67 | 0.91 | 0.60 | F(2,71)=0.46 | Not sig. |

(v) Marital status
Chi-Square test:

| | CFS | Normal | Chronic | Row Total |
|---|---|---|---|---|
| divorced | 5 | 1 | 1 | 7 |
| married | 23 | 16 | 11 | 50 |
| single | 17 | 19 | 10 | 46 |
| status not given | | 5 | 1 | 6 |
| | -- | -- | -- | -- |
| Column | 45 | 41 | 23 | 109 |

Chi-Square ignoring missing data (4 d.f.) = 3.46, Not significant at 0.05 level

(vi) Sex
Chi-Square test:

| | CFS | Normal | Chronic | Row Total |
|---|---|---|---|---|
| female | 31 | 32 | 15 | 78 |
| male | 14 | 9 | 8 | 31 |
| | -- | -- | -- | -- |
| Column | 45 | 41 | 23 | 109 |

Chi-Square (2 d.f.) =1.46, Not significant at 0.05 level

This should mean the CFS group does better on cognitive tests, i.e. biasing results in favour of the null hypotheses. Levene tests on the age and IQ distribution show no significant difference in variance between groups.

Employment

Of the CFS group, significantly less were working than controls (see Appendix 3 Table 2Ia). A breakdown of the figures for the CFS group (shown in Appendix 3 Table 2Ib) shows that a substantial number (10) had stopped or had lost work directly due to the illness, and of the other CFS patients not working, most were impatient to return.

CFS-related jobs

Of the group of CFS patients, three were nurses and four were teachers, professions linked with CFS (see Section 1.6 of "Literature Survey"). This is not a high enough number to confirm that these are CFS related jobs.

### 4.2.2 Illness Variables

CFS patients initial illness

The CFS patients differed in whether they had been ill with a particular illness which leads into CFS. Of the 47 patients in the study, the following pin-pointed a definite illness at the start of the CFS process:

2 had suspected meningitis

10 had Coxsackie B

7 had Glandular fever

1 had pneumonia and peritonitis.

Contact with trigger illnesses

The literature suggests that contact with a trigger illness may start CFS. Subjects were marked for number of contacts, prior to their illness, with Coxsackie B, glandular fever (EBV) or CFS itself. The mark was derived by adding up the number of close contacts

prior to their illness (e.g. family or close friends) and minor contacts (weighted 1/2) to give a score for contacts. In Appendix 3 Table 2G the distribution of contact has been scored as yes or no: i.e. whether or not the person had had any contact with related illnesses. All data collected retrospectively had methodological problems, and therefore this is a very rough measure. For example, a problem with this method is that CFS patients have become aware of the existence of CFS as an illness and are therefore more likely to find out or remember others with the illness. The Table shows the distribution in CFS subjects as roughly 2/3 having had contact and 1/3 not having had contact, with the control groups having the reverse of that pattern. This distribution was significant on a chi square test at the 0.01 level (chi-squared=10.5 with 2 d.f.).

Previous serious illness

The three groups were compared to see if they had similar numbers of subjects with previous serious illness, i.e. any illness or condition on their medical record considered by the consultant to be serious. The procedure was that any illness that was unusual or known to be serious or an unusually severe infection or long term medical condition was marked on their research notes provided it was disclosed in their notes or by themselves. Then unless the illness was considered non serious on consultation with the consultant it was counted in this category. A list of serious illnesses was not used because only by looking at medical notes could one take into account the severity of a condition in a particular patient, and because the consultants were in infectious diseases and were therefore well aware of what illnesses are considered serious. This does however make it harder to define criteria and to replicate the study. The percentages who had had serious illness in the past is shown in Appendix 3 Table 2F. This shows more serious illness in the CFS group (34%) that in both control groups (5% for normals and 20% for Crohns/colitis subjects) which is significant on a chi square test (chi-squared=10.9 with 2 d.f., $p<0.01$).

Length of illness

The length of illness of the CFS and Crohns/colitis patients showed slightly different

patterns and this is shown in Appendix 3 Table 2H. As discussed elsewhere recovery occurs in CFS spontaneously in the majority of cases, while in Crohns/colitis patients recovery is more spasmodic. It is not, therefore, surprising that only 18% of CFS patients have had the illness for five years or more, compared to 45% of Crohns/colitis patients. There is no reason to suspect that this distribution of length of illness in the two groups does not represent the distribution in the clinic population of each group. As the literature to date (Spracklen 1988) suggests, only a small proportion of CFS patients have CFS for longer than five years. The early 1980's in Glasgow saw a number of reports of outbreaks of CFS (Keighley and Bell 1983; Behan 1985). It is interesting, therefore, that these patients do not now dominate the present CFS population in the Glasgow area.

### 4.2.3 Symptom Variables

#### Fatigue

The three groups indicated on a scale 1-10 (exhausted to energetic) how tired they felt (see Appendix 2 Item 7). The group distributions (Appendix 3 Table 2C) give an indication of fatigue in the three groups. CFS patients' mode score was 2, in the chronic group it was 7 and in the normal group it was 9. CFS patients' scores are distributed toward the exhausted end of the scale and normals towards the energetic end with Crohns/colitis group being in several peaks. The mean for the CFS group was 3.22 compared with 6.39 for the normal group and 5.56 for the Crohns/colitis group. Table 6 shows that the CFS patients are significantly ($p<.001$) more fatigued than both normal and chronic controls.

#### Symptom list

The three groups filled in a comprehensive list of symptoms particularly associated with CFS. However, because of the nature of CFS, the symptoms covered were mostly those that could be described as common symptoms; the questionnaire is given in Appendix 2 Item 7. The symptoms were each rated 0-3 and the scores added up to give a total.

The distribution of scores for symptoms during the week before testing for this list are given in Appendix 3 Table 2D.

The control groups had no subjects reporting more than 50 symptom points; 33% of CFS patients scored above this number. 48% of Crohns/colitis and 46% of normal patients scored less than 5 symptom points while only 4% of CFS patients did. Of the symptoms reported the CFS group reported a significantly higher amount of problems with memory or concentration. The mean for the CFS group was 37.93 compared to 7.63 for the normal group and 7.70 for the Crohns/colitis group. Table 10 below shows that the CFS patients are significantly (at least $p<.01$) reporting more symptoms or greater severity of symptoms than both normal and chronic controls, for both that time and that week.

Depression

The amount of depression in each of our groups was important to the study. Although subjects with a psychiatric history or on antidepressants had been excluded in all groups, the amount of depression in the included subjects still varied considerably. Appendix 3 Table 2E shows the distribution of scores on the Centre for Diseases Depression scale. A 16 point cut off score, above which depression is deemed to require treatment, has been accepted for this scale (Comstock 1976). The table is divided to show separately the sections of the populations scoring over this level. Sixty percent of the CFS group scored 16 or over compared to 5% of Crohns/colitis patients and 14% of normal subjects. At the other end of the scale 50% of Crohns/colitis patients and 46% of normal subjects compared to 7% of CFS patients scored 5 or less on the depression scale (see Section 4.4.1 for more discussion of this scale).

Summary of 4.2

The population profile of the groups was similar for age and IQ, with slight differences which have been mentioned, and would mean the results would be biased towards the null hypothesis. There was a high female to male ratio in all the groups. Marital status

and number of children were similar in all groups. The CFS patients had a high number of depressed subjects, more previous contact with trigger illnesses and higher amounts of previous illness than both control groups. The CFS subjects had a much higher number of symptoms ('per week' and 'at the time') and higher fatigue level. The Crohns/colitis patients had, on average, been ill longer than the CFS patients. All these factors could have been predicted from the literature and fit in with the profile expected of CFS groups.

## 4.3 Recovery and repetition effects

### 4.3.1 Recovery

Patients with CFS show a typically relapsing progress (Wookey 1986): they appear to recover gradually over time, without intervention, with relapses occurring less and less frequently. It was expected, therefore, that CFS patients would initially be slightly worse on cognitive testing but improve as they recovered, beyond practise effects. Repeating the cognitive testing during recovery showed us the changes that were taking place during the course of the illness. It enabled the plotting of such change and to compare it to other factors such as mood.

### 4.3.2 Repetition: test and re-test validity.

Most of the memory tests were not repeated in the same version consecutively because they would lose validity and to reduce practise effects (Logical Memory, Associate Learning, Digit Span, Rey Complex Figure and Visual Span). Reaction time tests in the same form are expected to be reliable over time (Cronbach 1964); it was expected that these tests would not show improvement over time in the control groups. Digit Symbol, however, is a test known to be subject to practise effects (see repeat testing of WAIS/WAIS R, Matarazzo and Herman 1984) and the Stroop and Block Design were

expected to be sensitive to practise. It was expected that all groups would show practise effects on these tests but that improvement would only be considered to have taken place if a group exceeded the improvement of other groups. The Threshold Task, PASAT, Word recognition and the Word Fluency tests also used differing versions.

### 4.3.3 Using different versions on some tests.

The test/re-test design involves some other methodological problems. Some tests, mostly those involving simple memory, cannot be reused using the same version of the test. Logical memory for example would lose face validity if the same passage was given to be remembered, since we might be tapping a different memory storage and encoding from the first reading and not just memory from the second reading of the passage. It is not normal practise to repeat the same memory test within a short space of time unless intervention has taken place or the subjects' memory is so poor that such considerations make no difference. The tests have, therefore, to be varied and allowance made for the different versions in the analyses of the data. Retest with different versions is a standard technique as discussed by Golden et al. (1990)(p30).

It was expected that by counterbalancing versions and adjusting analysis for version if necessary, the effect of using different versions would not influence the results in any way. (The distributions and different scoring on versions were to be examined to check that any effect of version was controlled for.) The different versions were used in similar proportions in each group.

## 4.4 Mood factors

### 4.4.1 Depression

The patients may experience loss of performance due to factors other than the illness itself. Depression and anxiety levels have been shown to be high in CFS (see section

3.1, Literature survey) so their effect may be the cause of changes in cognitive performance. "Clinically diagnosed depression can have a significant impact on information processing and individuals with elevated symptoms of depression perform more poorly on cognitive tests" (Miller 1975). In looking at test performance, therefore, anxiety and depression need to be controlled for. The design quantified and allowed the effect of these variables to be analysed, and the changes to them over time monitored.

While it has been shown that depression is common in CFS, the direction of causality is not known. Taerke et al. (1987) suggest that the majority of CFS patients are suffering from clinical depression. However, the level of depression rating they use is very low and they use scales with a high somatic element that may confuse the illness's symptoms with those of depression. In this study, ratings on a relatively low somatic depression scale are taken to decrease the overlap in the physical symptoms of CFS and depression questions. This depression score indicates a level of current depressive symptomatology; as such it gives an ordinal scale over all groups suitable for group comparisons. Although the scale is not a diagnostic tool for major depressive disorder, the scale has been shown to differentiate those who have major depressive disorder (Somervell et al. 1993) . It has also been shown since the study reported in this thesis to differentiate between fybromyalgia patients who come out as more depressed than both rheumatoid and other clinical patients (Hawley and Wolfe 1993).

4.4.2 Anxiety

There is evidence that CFS patients have higher than normal anxiety scores. Anxiety is known to affect concentration and increase distractibility generally (American Psychiatric Association 1980) and these affect performance on cognitive scales. Corcoran (1989) links anxiety and depression in epileptics to high complaints of serious memory difficulty. Richardson (1988) suggests that similar complaints in Pre-Menstrual Tension are due to anxiety. It is useful therefore to look at anxiety levels in patients to see if this may account for differences in subjective and objective ratings of cognitive performance.

## 5. Choice of tests

### 5.1. Tests used

Table 4 shows the tests used in the study.

### 5.2 Reasons for test selection

The tests were chosen because they are tests which have revealed diffuse minor neurological problems: in minor head injury (Dikmen et al. 1986(a) and (b)), in epilepsy patients (Gillham et al. 1988) and in alcoholics (Wilson et al. 1988) and toxic poisoning cases. The literature describing patients' complaints indicates that CFS patients complain of problems which overlap with these groups' problems, i.e. loss of memory, concentration and verbal fluency (see Section 1.5.2 in the literature survey). Pre-morbid IQ level was controlled for by using the NART for group comparison but examination of verbal IQ has not been central to this study because it is not expected that deterioration of verbal IQ is a major problem in CFS.

Selection of each test occurred for one of four main reasons.

1. The test was a commonly used standardised test of an aspect of neuropsychology and there was evidence to suggest that this aspect is affected by CFS.
   Where a choice of similar and equally suitable tests were available the most widely used were chosen. Given the constraints on the length of session, tests which took a shorter time were preferred.
   Tests: Wechsler Memory Scale, Reaction Time, Finger Tapping, WAIS Digit Symbol and Spielburger Anxiety Questionnaire, Health Locus of Control Questionnaire.
   An exception is the CES-D which is not the most obvious depression scale but was chosen because it seemed to have least overlap with physical symptoms. At the time it was scarcely used in the field but now has become widely used (for example, the Science Citation Index has shown around 60 references to CES-D in the last 3 years,

**Table 4: TESTS USED**

National Adult Reading Scale NART (Nelson and Mckenna 1975)

Cognition

Verbal Memory
Logical Memory, Associate Learning, Digit Span subtests of:
- Wechsler Memory Scale Form 1 (Wechsler 1945)
- Wechsler Memory Scale Form 2 (Stone and Wechsler 1946)

Word Recognition Task (Lezak 1983 pp.620-621)

Spatial Memory
Rey Complex Figure (Rey 1941) and Taylor Complex Figure (L.B.Taylor 1979)
WAIS Block Design (Wechsler 1955, from Wechsler Adult Intelligence Scale NFER 1957)
Visual Span (Wilson et al. 1988)

Reading and Word Finding
Word Fluency (Spreen and Benton 1969)
Stroop task (Stroop 1935; Perret 1974)

Psychomotor Speed
Choice Reaction Time (Van Zomeren 1987)
Finger Tapping (Halstead Reitan Neuropsychological Test battery: Halstead 1947)

Speed and ability
P.A.S.A.T. (Gronwall and Sampson 1974)
Visual Change Detection Threshold (VCDT) (Wilson et al. 1988)
WAIS Digit Symbol (Wechsler 1955, Form Wechsler Adult Intelligence Scale NFER 1957))

Mood and Symptom Questionnaires

Centre for Epidemiological Studies Depression scale (CES-D: Radloff 1977).
State-Trait Anxiety Scale Form X (Spielberger et al. 1970)

Fatigue on a 1-10 Likert Scale (Likert 1932)
Symptom List (Wookey 1986)

Psychiatric and Stress variables

Multidimensional Health Locus of Control (MHLC) questionnaire Form B (Wallston and Wallston 1978)
Middlesex Health Questionnaire (MHQ) (Crisp et al. 1978)
Beliefs about Illness scale based on Michielutte and Diseker (1982)
Short list of major life events (Paykel 1972)

mostly in the areas of psychology and medicine).

2. The test was a new test which had highlighted deficits in other groups with similar problems.

   Tests previously used in epileptics and alcoholics to show visual memory, attention and signal detection problems (Gillham et al. 1988; Wilson et al. 1988).

   Tests: Threshold task, Visual Span.

3. The test was not necessarily normally used in a neuropsychological test battery but it measured a particular neuropsychological problem which is indicated in the literature as a problem in CFS patients.

   For example, CFS patients have been said in the literature to have particular problems such as in word finding, and confusion of words which sound the same e.g. black and blue.

   Tests: Word Fluency, Stroop, PASAT.

   Questionnaires were also designed or adapted to cover specific problems in CFS patients e.g. General Questionnaire and Beliefs about illness questionnaire.

4. It was a standard test which was being used to fill in a gap in the battery for a general neurological assessment.

   Tests: Rey memory, WAIS blocks.

Alternatives to the WMS would be to use a battery including these kinds of variables such as the Halstead Reitan Battery (HRB) (Halstead 1947; Russell et al. 1970) but none of these would have been tailored to CFS patients in particular.

## 5.3 Testing different aspects of neuropsychological functioning

### 5.3.1 Introduction

This battery of tests was used to measure the main aspects of intellectual function. Tests are described in the following Section. Questionnaires and score-sheets are given Appendix 2. Permission has been sought from the authors.

### 5.3.2 Testing memory

Tests from the Wechsler Memory Scale and WAIS were used. The Wechsler Memory Scale version used was the original 1955 version rather than the new WMS-R (Wechsler 1987) because at the time of the design of the study, in 1988, the WMS-R was only just coming on to the market and therefore it had not been validated by use in different test situations. The WMS was used rather than the WAIS verbal subtests to test memory because they are more suited to testing diffuse brain damage than tests primarily aimed at testing verbal IQ which does not normally deteriorate in these type of conditions. The WMS also had the advantage of having alternative versions available that were standard and had been used in this way before (Stone and Wechsler 1956).

(i) Verbal memory.

Wechsler Memory Scale

Memory tests included parts of the Weschler Memory Scale (WMS). It is universally used and is well validated and standardised (Wechsler 1945). The Wechsler Memory Scale is a short scale comprising a number of different components: it can be used complete or in component parts. The parts used were Logical Memory passage, the Digit Span and Associate learning component tests. The Logical Memory and Associate learning involve new learning as well as memory. They are therefore sensitive to the kind of problems found in toxic poisoning by alcohol, barbiturates etc. which may be similar to CFS effects.

It was not felt necessary to complete the whole scale since that would have involved giving tests well within the subjects ability and which may even have been so easy that they regarded them as derisory. The tests were given in standard procedure although more modern language was sometimes used.

WMS subtest - Logical Memory

The Logical Memory test involves the tester reading a short passage to the subject. The

subject then has to recall the passage as exactly as possible and is given marks for correct words and phrases. The Wechsler Form 1 and the Wechsler Form 2 have four different passages, an easier and harder passage for each. The passage could not be given twice to the same patient because that would have changed the nature of the test, that of immediate recall: residual memory from the previous session and recognition memory might produce different results from the immediate recall of the passage done at first testing. Therefore three of the passages were given at different times over the 1st-3rd testing. Form 1 Passage One was given using the slight alterations normally used in Glasgow (Appendix 2 Item 3).

WMS subtest - Associate Learning

The Associate Learning test involves remembering six usual and four unusual pairs of words. The subject is read the list of pairs three times; after each time he/she is asked the right pairing for each word. Both versions of the Wechsler Form 1 and 2 were used; the subjects were given either version 1 or 2 to start then the other version on second testing and the first version was repeated if they came for a third testing. Form 2 was designed to be used as an alternative to Form 1 (Stone and Weschler 1956). Getting more hard than easy pairs is thought to show malingering according to Lezak (1983 p.620). This test was also used as an indication of whether CFS patients had learning deficits which might cause CFS patients severe difficulties in normal living. The test was administered according to the advice given in the instruction manual (Wechsler 1955). The score is 1/2 for a correct easy answer and 1 for a correct difficult one.

Word Recognition

The word recognition test used was based on a test reported in Lezak (1983 pp.620-621). This test is designed on the premise that recognition is easier than recall. Subjects are read 15 words and then asked to tick ones they heard from a list including the 15 which had been read to them and 15 similar words. Word recognition tests should confirm the differences between CFS patients and normal subjects but the differences should not be very different from results in other memory tests. Word recognition could

also be used to test how accurate CFS patients were in their answers by taking marks off for errors in recognition. This test was retested by giving a different selection of the 15 words so ruling out any advantage (indeed making it a slight disadvantage) to remember the previous set. This test is very quick and was chosen over other recall tests because of its speed of administration and because the equally quick Williams test (Williams 1968) (also considered) was concerned with visual recall rather than verbal, and visual recall was thought likely to yield less useful results.

WMS subtest - Digit Span

The Digit Span test involves recalling, in order, strings of numbers (4-7 in length) (digit forward) and recalling strings (3-6 in length) in exactly reverse order. The numbers are never repeated in the same string.

(ii) Visual-spatial memory

Although CFS patients' problems do not normally include those of spatial memory, to leave spatial memory out completely would be to have an incomplete test battery of memory. In any case one is then able to compare the relative performances of CFS and controls on both tasks to see if they are inconsistent. The spatial memory task of the Weschler memory scale, however, was not used; instead the Rey and Taylor Complex Figure task was chosen.

Rey/Taylor Complex Figure

The Complex Figure was chosen as being a more difficult spatial memory task than the WMS visual memory task, with the potential for finer grading of spatial memory ability. It was of sufficient difficulty that subjects were unlikely to ceiling on the task, which might have happened had the Wechsler Memory Scale component been used. The Rey task tests perceptual organisation as well as memory. Besides the scoring of the Rey, a piecemeal approach to the diagram is also an indicator of possible problems organising material.

Beaumount and Davidoff (1992) suggest that the Rey-Osterreith Complex Figure (Osterrieth contributed the scoring method used in this study) is the best of the copying tests partly because of its high reliabiltiy of scoring.

There are several ways of administering the Rey Memory Complex Figure task. In this case, the subjects were given a hard memory task, that is after copying the Rey or Taylor Figure they were given 15-20 minutes on other tasks and then asked to recall the diagram. The Taylor and Rey Complex Figures were both used since their design elements are matched; subjects were randomly given one version at the first session and then given the Figure they had not used at the previous session. Instructions given to the patients were as standard.

Visual Span.

This is a computerised test of retention of visual information. The method of testing this aspect of memory is new. The subject is presented with a pattern of blocks of increasing complexity; he is presented at a timed interval with the pattern altered by one block and has to point to the change. The subject's score is the largest number of boxes on the screen prior to making two consecutive mistakes; ceiling score is 28. This test has been used to identify memory problems in alcoholics and epileptic patients. It shows how well the subject can recall a complicated pattern.

5.3.3 Testing language problems

Stroop

The Stroop task has been used to measure a number of factors: reading fluency, distractibility, mental control and response flexibility. It is particularly good, for this study, because it tests a specific problem of CFS patients described in the literature, viz word confusion, giving a different word with similar sound and or meaning such as blue instead of black (Ramsay 1981). The test of the Stroop effect used was similar to trial II and IV

of the original. One card was used: it was a card with words in different coloured type, the colour being different from the colour word (RED BLUE GREEN YELLOW BLACK); there were 16 lines of 5 words. A copy of the card is shown in Appendix 2 Item 10. The subject was asked to 'Read the words on the card as fast as possible without making mistakes'. This was timed, errors were not penalised directly in the timing, subjects seldom made mistakes and when they did they penalised themselves by hesitation or correcting the mistake.

After the first 10 CFS subjects it became clear that the CFS patients did not find this task difficult and it seemed unlikely that any differences would be found with controls (although later analysis proved there was a difference). Therefore in order to increase the difficulty of the task a harder task was added: when they had completed the task they were then asked to 'Call out the colour names on the card not the words. Like this.' The experimenter then called out the first line of colours on the sheet in order. The reading of the colours was timed in seconds.

### 5.3.4 Testing psychomotor skills

#### Choice Reaction Time

This is a standard reaction time task: the subject was required to press a button next to one of 4 lights when a light came on. The four lights were arrayed in a fan about six inches from the movement sensitive button on which the subject put his hand. Next to each light was another movement sensitive button onto which the subject had to move his hand. Appendix 2 Item 4 shows the layout of the box. The reaction time box was plugged into the computer which recorded and calculated means of decision and movement time. The subject's decision time was measured by when his hand left the start button and his movement time by when he hit the correct button next to the light that went on. The subject was given a very short practise because of the problem of tiring the CFS patients.

The first test run cued the subject (by sound and light) randomly 20 times for each light. This gave enough reaction time movements to be sure to get a reasonable measure; it was however deliberately shorter than it might have been in order that the CFS patients did not get too tired. The test was re-run straight afterwards to measure if the CFS patients were slowing at the task; this time ten sets of the four lights were randomly displayed. This test gave measures of time taken to initiate action ("Decision Time"), time of neuro muscular movement ("Movement Time") and a measure of fatigue.

Other reaction time tasks could have been used, such as the simpler single reaction time task where the subject responds to the same stimuli on each occasion (e.g. one light not four) or more complicated tasks where the subject responds indirectly to the light or has to press their response in sequences. The first would have been too easy for our subjects and the second type would have unnecessarily complicated the results.

Finger tapping

The Finger Tapping Task consists of the subject tapping a calculator for one minute. The calculator, a Casio College fx-100, is set to continuous addition (by pressing 1++0). The test was used as a measure of speed, co-ordination and fatigue. This test was simple and quick and is frequently used as part of a test battery. The experimenter felt that this could be used as a test of muscle fatigue without it being injurious to the patients. If muscle fatigue was produced in the larger muscle groups then it could have a prolonged injurious effect as muscle of CFS patients may take much longer to recover after exercise.

Digit Symbol

The Digit Symbol test involves turning numbers into a symbol code which is given at the top of the test. The digit symbol measures information processing ability and speed. The test was done twice with the same code because if the code had been changed it would have been difficult to standardise to the existing version. In fact, subjects did not seem to remember the code well from the first time. Considerable practise effect was

expected on this test because of reuse of the code and the subject learning how to approach the task. This task was used because it was felt that it might yield results on the problems of information processing at a higher level and at speed.

5.3.5 Testing attention and signal detection

P.A.S.A.T.

P.A.S.A.T is a test of divided attention. Subjects have to add up and give the answer to the addition of each pair of consecutive numbers; they have to use each number twice and hold the previous number in their head while giving the addition to the sum. The task requires concentration and inhibition of the previous answer. This test was quite difficult to grasp so detailed explanation and practise was given until the subject could answer the practise questions in the right way before commencing. The subject was presented aurally with a succession of random numbers between 1 and 9. The subject had to add each number to the next number and give the answer. This was explained using pencil and paper to show what kind of number would be given and what the answer should be. Then the subject attempted to do the practise part of the tape where a random sequence of a few numbers were given. The practise part and test part numbers were presented at a speed of 1.6 second intervals. Two different sequences of numbers were used for different presentations. The score was the total number correct out of 60.

This task was used because it was suggested as a task of possible interest in Kilfedder's (1988) study. The use of distraction with this task was originally thought of as a progression on Kilfedder's work but rejected as being too difficult for subjects.

Visual-Spatial abilities

Block Design WAIS subtest

The Block Design subtest is a constructional task which tests visual spatial abilities. In this, the subjects are asked to reproduce a pattern of squares and triangles using blocks

each of which have two red faces, two white faces and two faces with triangles of red and white (see Appendix 2 item 6). The test consists of 6 patterns of 6 easier blocks and 4 of 9 harder blocks to be made from a diagram. Once the solution to a pattern is found it is easy to reproduce the pattern again; therefore subjects who did all the blocks on first testing were not asked to repeat them but were regarded as having reached ceiling. All subjects completed the same simple designs. Some subjects were able to complete all the designs and those subjects who failed to complete all the designs were given the opportunity to redo the harder designs at second or third testing. The test was chosen as a good test of visual spatial abilities in two dimensions and Beaumount and Davidoff, in Crawford's handbook of Neurological testing (1992), say of WAIS Blocks that it is the 'clear choice of a test of this type'. (p.124). The instructions given to the subject were as standard in the test manual.

Visual Change Detection - Threshold Task

This task has shown up differences in alcoholic patients (Wilson et al. 1988) and has also been used with epileptic patients (Gillham et al. 1988). It shows how well the subject can pick up small changes at speed. It was selected to see if CFS patients were slow at perceiving input as well as responding to stimuli as in Reaction Time Decision Time (RTDT) and Reaction Time Movement Time (RTMT). The task should pick up problems of information processing at speed (Gronwell 1977). The question of central fatigue is important in the case of CFS. Visual threshold tasks of this nature have a high performance workload and need high concentration. As Grafman et al. (1991) say, if CFS patients do worse on vigilance tasks this could be attributed to attentional deficit due to central fatigue.

The Threshold Task is displayed on computer. A randomly generated array of an average of 50 boxes out of a regular 10x10 display is displayed (the size of the array is 185mm x 105mm). The result is a random scatter pattern on the screen. Each box is 5mm x3mm. One box is presented after a delay (starting delay is two seconds). The

subject has to say which small box on the screen is presented slightly later than the others. With each correct response the delay is 20 milliseconds faster. The computer calculates the speed at which the subject regularly fails to pick out the new box (i.e. sixteen occurrences of a correct next to an incorrect response or vice versa). The threshold score is the estimate of milliseconds needed for the subject to get 50% of tasks correct.

Testing for fatigue during the Reaction Time Test.

It was thought that CFS patients might show an increasing reaction time during testing as CFS patients complain of early fatigue of muscles and cognition. To test whether this occurs the reaction time test was conducted in two parts. The reaction time test consisted of:

a) practise 1x4 trials only so as not to increase fatigue; score not taken

b) then a set of 20x4 trials reaction time

c) then a second set taken immediately after the first of 10x4 trials reaction time.

The median of the first set was used as the Reaction Time score and the median of the second set was used to measure the effect of speed changes during testing. Only 10 Crohns/colitis patients had time to complete the second part of the test, so this group therefore could not be used in a statistical analysis. The expectation was that, because people had little practise and normally get faster at the reaction time task, the second set would be faster than the first set for normal controls but not necessarily for CFS patients. Note that median scores for the set of reaction time scores were used, not mean scores, so that odd lapses of attention did not influence the measure.

5.3.6 Testing functionally induced poor performance

In order to rule out subconscious or deliberate distortion by the patients a simple test for functional malingering was included. The 15 item test (Lezak 1983 p.619) was given, to the first group of CFS patients. In this test the subjects are shown five rows of 3 sequenced figures. The rows are easy to remember but the experimenter emphasises

the difficulty of remembering 15 items. The subject is asked to recall the 15 items. Patients with functionally induced deficits are expected to fail to remember all the items. Of the 10 CFS patients who did the test none forgot any of the items. The 15 item test was so easy to subjects that some found it derisory and none were convinced it was difficult; for this reason it was discontinued. The Associate Learning test (as described above) was also used and results were scanned for scores where subjects scored better on hard than easy pairs; this did not occur in the CFS subjects.

Frontal lobe dysfunction

In view of the fact that fatigue in CFS patients could be related to lack of initiation of action and, therefore, be related to frontal lobe dysfunction, it was decided that some tests should be aimed at this aspect of brain function. Tests thought to be sensitive to such dysfunction in the battery include Stroop, Word Fluency and Block Design.

5.3.7 Choice of questionnaire: psychological tests and symptom recording procedure

The CES-D scale (Appendix 2 Item 5) and the Spielberger State/Trait Anxiety scale (Appendix 2 Item 11) were filled in at each time of testing together with the symptom list and fatigue scale. A set of questionnaires was given to patients at the first testing which they returned by post. These were the Health Locus of Control (HLOC) (Appendix 2 Item 12) scale, Middlesex Health Questionnaire (MHQ) (Appendix 2 Item 13) and illness questions (Appendix 2 Item 8). They were completed only this once between first and second testing. HLOC and illness questionnaires were used to look at differences in attitude between the groups that might relate to their illness. The MHQ scale gave an indication of psychiatric profile.

CES-D Scale

The CES-D Scale of Depression was used. This is a very quick and straightforward scale used by the Centre for Diseases Control in America. The reason it was chosen was because it was made up from cognitive questions about depression from other scales

(Beck 1961; Zung 1965; Dalstrom 1960 and Gardner 1968, all from Radloff 1977) and is therefore a very highly cognitive scale with minimal somatic content. This means that the scale is least likely to be recording general illness symptoms rather than depression Foelker and Shewchuk 1992 show the CES-D to be relatively unbiased by the patient's somatic complaints. The CES-D also has the advantage of being quick to administer so it can be included at each testing without any difficulty. Although it gives only a depression score not a clinical measure of depression, it has been shown to have high sensitivity to major depression as scored on the Lifetime Version of the Schedule for Affective Disorders and Schizophrenia (Somervell, et al. 1993). The CES-D has been used with large populations and a score of 16 used as a cut off point for clinical depression. Its validity is discussed in Radloff (1977) and Radloff and Locke (1986). The form used was similar to that shown in Appendix 2 Item 5, except that clients received copies with boxes instead of scores and they were asked to tick one of the boxes. Other scales considered were Becks's Depression scale or the HADS Scale; these were much longer and more somatic.

The Spielberger State/Trait Anxiety Scale

This is a simple questionnaire using describing adjectives to ascertain a person's anxiety levels. It has a measure for shorter term anxiety 'state' and longer term 'trait' anxiety. It is quick and straightforward to administer and so could be included at each testing. It has been widely used and standardised (Spielberger et al. 1970) and is highly reliable. The Form X was used. See Spielberger (1970) for Test and Scoring.

Middlesex Health Questionnaire

The MHQ is a straightforward questionnaire widely used and standardised. It is designed to measure general mental health. Its scales are designed to measure depression, anxiety, obsessionality, somatic propensity, phobic problems and hysteric propensity. All the scales correlate well with blind psychiatric interviews except the hysteria scale which seems to measure more extrovertness and sociability (Crockett 1969; Crown 1974). The purpose of their scale was to ascertain if the CFS group during their illness

were demonstrating psychiatric distress. See Crisp et al. (1978) for questionnaire and marking scheme. The subjects completed the questionnaire before or between testings, not under supervision.

The General Health Questionnaire was considered instead of the MHQ as a scale of psychiatric well being, it is shorter to complete but was rejected on the grounds that it was far less specific in the kind of results it produced.

### 5.3.8 Illness and Psycho-social data

#### Questionnaire

The general questionnaire given to the subjects was done with the experimenter. It asked demographic data: how old, whether working, whether married and if they had children. It includes data about the illness (if CFS or Crohns/colitis): how long the person had been ill, how long to diagnosis, had the doctors been helpful, what drugs was the patient on? It includes data about vulnerability: had they had a previous serious illness, had they taken lots of antibiotics prior to the illness and also what life events occurred in the 18 months before the illness? It also asked about activity prior to the illness (high physical activity being associated with vulnerability to CFS) and during the illness (CFS is associated with much lower activity). We also asked subjects to rate their illness against other illnesses.

#### Symptom data

In order to ascertain how subjects felt about their health at the time of testing, a symptom list was used (based on Wookey 1986). The symptom list excluded some of Wookey's items on the grounds that they were very subjective or not relevant for the purposes of this study knowledge. For example feeling awful, legs feeling heavy, clumsiness and difficulty in carrying things are aspects of the illness that are a result of other symptoms rather than symptoms in their own right. Looking pale and grey was left out because the patient did not experience it and received that knowledge from others second hand. Crying a lot was left out as depression was already included. Symptoms specific to

women were left out as we were comparing women and men together, i.e. flushing and vaginal discharge (see Appendix 2 Item 7 for form used).

Fatigue was measured on a 10 centimetre line, one end of which registered Exhausted (score 1) and one end Energetic (score 10). The subjects were asked to put a mark where they felt they came between the two ends of the Likert scale - see the end of symptom list in Appendix 2 Item 7 for this scale.

Life events

Patients were questioned about the highest scoring life events (Paykel 1972): births, marital status change, illnesses and deaths in the family, prolonged stresses, job and house change. The number of these high scoring events was recorded. Papers showing links between illness, immunity and life events (Solomen et al. 1979) feature bereavement as the most prominent link. Two papers have shown a correlation between life events and CFS: Stricklin et al. (1990) and Wood et al. (1991) found CFS patients to have significantly more, or more serious, life events pre-illness. In investigating life events in patients prior to their illness it was decided to concentrate on a short list of major life events for two reasons: the inclusion of all life events would have made the questionnaire a) too long and b) subject to distortion, since minor life events are recalled more frequently if they have happened recently according to Davies (1992).

Health Locus of Control and beliefs about illness.

The aetiology of CFS is still under debate; it is possible that several psycho-social factors may relate to onset or to duration. In CFS much lip service has been paid to the idea that it is stress related, especially in the media. This idea has been little examined and this is why some work has been included on it now. The degree of stress one experiences has been related stressful events (some of this can be tested by life events) personality in relation to beliefs about stress (this can in part be tested by locus of control) and beliefs about the situation (we are looking at this by testing beliefs about illness in the subjects). Ability to cope with pain and chronic illness has also been

associated with locus of control (Phares 1962; Reid 1984). It may be a contributing factor in depression and illness adjustment. Not only may external locus of control hinder coping with the illness but Skevington (1983) shows that long periods of illness may alter beliefs about locus of control. Powell, Dolan and Wessely (1990) show that CFS patients tend to attribute their symptoms to an external cause compared to a depressed group who tend to attribute them to internal causes. Whether this externality of control is prevalent in CFS patients will be seen by looking at their locus of control beliefs in health matters. Whether CFS patients have particular problems in adjusting to their illness will be considered by comparing them to Crohns/colitis patients on measures of health locus of control and health beliefs. Locus of control beliefs could also be contributory factors in depression.

Health Locus of Control

This scale is a development of the Locus of Control scale by Rotter et al. (1962); it is given in Wallston and Wallston (1978). It is designed to find out how external is the subjects beliefs in relation to health i.e how much subjects attribute the quality of their health to external factors. It gives three scales of types of belief: 1) to oneself 2) to powerful others (like doctors) and 3) to other external forces (like chance). It has been examined in relation to other scales of this type (Wallston and Wallston 1978). It is particularly useful to test patient populations.

Not only may external locus of control, as discussed earlier, hinder coping with the illness but Skevington (1983) shows that long periods of illness may alter beliefs about locus of control. Powell, Dolan and Wessely (1990) showed that CFS patients tend to attribute their symptoms to an external cause, compared to a depressed group who tend to attribute them to internal causes. Whether this externality of control is prevalent in CFS patients will be seen by looking at their locus of control beliefs in health matters. Whether CFS patients have particular problems in adjusting to their illness will be considered by comparing them to Crohns/colitis patients on measures of health locus of control and health beliefs. This questionnaire was completed unsupervised because it

was done by the subject at home between first and second testings.

Beliefs about illness

This set of Likert scales looks at the beliefs of the three groups about six illnesses: two are ME/PVFS/CFS and stomach ulcers, the other four are cancer, Multiple Sclerosis (MS), arthritis and a broken leg. These illnesses are chosen to include those concerned in the study and as examples ranging from mild to severe illnesses as shown on the seriousness of illness rating scale (Wyler et al. 1968). It is suggested in Abbey and Garfinkel (1990) that CFS patients over-exaggerate illness, by being somatically preoccupied; patients are possibly obsessive about illness. Similar scales were used by Cooper and Fraboni (1988) in order to survey people's beliefs about illness. Michielutte and Diseker (1982) used the scale to look at how children appraise cancer, and how children with cancer view cancer was examined by Jamison et al. (1986). The intention is to see if CFS patients are more negative than controls about illness in general and if they see people as more vulnerable to illness. The Likert scales were given to the subjects and they were asked to fill in how much they agreed or disagreed with the statement by marking a section of the Likert scale. These questions were completed unsupervised.

Two questions were combined in this study because they were felt to overlap considerably: they refer to the illness as 1) as powerful 2) as scaring people; thus only 5 questions were asked. See Appendix 2 item 8 for this version of the test; scoring is 1-7, with a score indicating a negative attitude being higher.

**5.4 Shortening the test battery**

The test battery had to be shortened for some subjects:

1) CFS patients who could not manage the complete battery;
2) subjects who did not have time to complete the whole battery; (this was usually due to a shorter time available due to consultants appointment or the subject stating

he/she could only spare a limited time);

3) Crohns/colitis patients were not all asked to complete the whole battery as this was not necessary and it was thought more important to increase the willingness of patients to take part.

Where the battery was reduced the same tests were omitted so that the numbers for the most important tests would be consistent.

Tests sometimes not used:

WAIS Block Design

P.A.S.A.T.

Appendix 3 Table 1 gives the proportions completing the tests. Note that the finger tapping scores were faulty for the first appointments, and Stroop Colours was not included, so these scores are not given for a number of CFS patients.

**6 Reasons for choice of longitudinal design**

A longitudinal design was chosen to examine how cognition changed over the process of the illness. Two main methodological designs are normally used to measure change over time. One is to compare different groups with the same attribute, e.g. CFS groups at different stages of their illness. (The most common form of this design is testing subjects of different ages). This would not be suitable for our purposes because individual differences (which exist in CFS severity) might outweigh the differences over time. The second method is by longitudinal design, a standard method which tests the same patients over time; this is not possible for a long time span in many circumstances. In this case it was quite practical to test the same patients at four-monthly intervals.

## 7. External factors

### 7.1 Place of testing

Patients were seen at Ruchill2 Hospital Infectious Diseases Department, Stobhill Gastroenterology Department and St Andrew Ambulance Headquarters in Glasgow. Those seen in hospital outpatients were seen in the day, those in the St Andrew's Ambulance building in the evening. Crossover between groups in terms of place and time was encouraged but there was not enough cross over to statistically control for place of testing. Most of each group were seen in the place they normally attended. The tests took place in a variety of different rooms although most of the hospital rooms were similar in size and lighting. Every endeavour was made to ensure that lighting was similar and adequate in all the rooms used, however variation of lighting occurred due to time of day and season and slight differences occurred in chairs and rooms. The equipment and procedure was similar at all locations. Occasionally subjects had to be tested concurrently in neighbouring rooms; procedures were kept similar with supervision via connecting doors.

### 7.2 Time of testing

The CFS and Crohns/colitis group were mainly seen during the day although a few of subjects from both groups came in the evening. The normal controls (except for two) were seen in the evening. It was intended that normal controls be seen when they were likely to be most fatigued and CFS when least fatigued so that they could cope with testing. It seemed appropriate to have tired controls so that the ordinary effects of fatigue could be reduced as the cause of any deficit in performance in CFS patients.

Time of day differences obviously occurred, although some overlap in time as well as place happened between the groups. CFS patients were not willing to be tested in the evening because they were too ill at that time; normal controls were mostly working and

therefore did not want to come to day-time appointments. Most of the normal controls took part between 6.30-10.00 p.m. at night after work, and were expected to be fatigued. CFS and Crohns/colitis patients took part between 9.00 a.m. and 5.00 p.m. Time of day differences would not occur between CFS and Crohns/colitis patients.

Wood et al. (1992) monitored energy in CFS patients over different time periods. He found 10.00-12.00 a.m. to be the highest energy time for CFS patients, and early morning and late evening to be the lowest. The controls followed the same energy fluctuations, but CFS patients, averages, were always lower in energy at any one time. This means that CFS patients were tested at peak energy level times and normals at lowest energy times, therefore favouring the null hypotheses.

### 7.3 Test Order

The tests were given in different orders to control for effects of the position of tests in the battery.

### 7.4 Length of testing

Patients were tested for approximately 1 to 1 1/2 hours per session and were tested on up to three occasions. Patients had been seen by a consultant prior to testing and assessed as fit enough to take part in the study. CFS patients took far longer to complete their test battery than normal controls; this occurred at first and second test sessions, although for both groups the second testing was shorter than the first.

### 7.5 Time between testings

The study was designed so that retest intervals should be four-six months. In fact, owing to problems with subjects not attending or postponing due to illness, the retest interval

had a wide range. Retest for CFS patients took place on average 5.9 months between first and second testing (standard deviation 2.8 months), 5.0 months for normal patients (standard deviation 1.3 months) and 3.3 months for Crohns/colitis patients (standard deviation 1.3 months). The longer recall of CFS patients was largely due to some very long individual retest intervals, for example 17 months (removing this patient leaves a mean of 5.5 months with a standard deviation of 2 months). In the case of one of the controls after such a long interval the experimenter was not able to retest the person, because the study was no longer running. Crohns/colitis patients also had to be tested three-four months after first testing to fit in with the available time at the hospital clinic. Subjects were seen when they could manage and therefore patients were seen serially at any time during the 3 years of the project irrespective of their group, providing that four months had elapsed since their previous testing.

We were interested in the improvement of CFS patients per se not over any particular time scale. The fact that CFS patients generally had longer between tests is likely to mean they benefited least from practise and results are under-stated.

## 8 Summary

The study was designed to discover:-

1) whether CFS patients were poorer on various neuropsychological tests;

2) whether this poorer performance improved with recovery from CFS;

3) whether the poorer performance could be accounted for by depression.

The design controls for factors such as differences in IQ between the groups. Information about beliefs, life events and activity have also been collected.

# CHAPTER 4. RESULTS

## Introduction

The CFS, Crohns/colitis and normal groups were compared in two main ways:-

1) The subjects' general activity, medical aspects of their history and psychiatric tests give a profile of the groups. This is considered in Section 2, "Results Part 1".
2) The subjects' performance on the neuropsychological test battery is compared. The performances at first and second testing are analysed and the effect of mood variables on scores is analysed. These points are considered in Section 3, "Results Part 2".

Tables of the findings are included in the text. Section 1 outlines the statistical approach taken.

## 1. Statistical analysis

### 1.1 Comparison of all three groups together at first testing.

The three groups need to be compared together. The F-test from ANOVA tests the null hypothesis, but does not pinpoint where the differences are, so a further test is needed to decide where the differences are. The comparison of three groups requires careful consideration when statistical methods are used. Separate analysis of each group with each other would weaken the reliability of the analysis, because the probability of one of the comparisons being statistically significant increases with the number of separate operations on the same means. The test chosen to show where the differences were was, therefore, the conservative *post hoc* Scheffe test. The Scheffe test gives the statistically significant differences for each combination of pairs but takes into account the number of comparisons being made. This kind of procedure, adjusting for the number of comparisons being made, reduces the likelihood of finding too many spurious differences.

## 1.2 Normal distributions

The use of parametric tests assumes that the variables are normally distributed within the groups, and that the variance is constant between the groups. In fact ANOVA, which is the test which was proposed to analyse most of the data, is robust in this respect except where distributions are extreme, a number of peaks occur within the distribution (e.g. bi-modal or tri-modal) or the distribution is highly discrete. Some of the variables used in the study might be expected to be at floor or ceiling, and this would upset their normality. Possible problems include:

1) outliers, usually in the CFS data which could justifiably be removed;
2) severely skewed distributions, which can be removed by using the log of results (for some variables, such as Depression, 1 has to be added first to avoid taking the Log of zero);
3) bimodal distributions.

In order to ensure that problems of non-normal distribution of scores do not occur, normality of scores was checked and, where appropriate, the data transformed. Normality is studied visually by inspecting the distribution, and quantitatively by looking at the skew and kurtosis. If either of these latter is significantly different from zero, then Normality cannot be assumed. Typically (see e.g. Tabachnick and Fidell 1989), a significance level of 0.01 is used, so a null hypothesis of a parameter being zero was rejected if it was more than 2.5 standard deviations from the mean. The Levene test is used to check for homogeneity of variance between the groups. Details of these tests on our data are given in Appendix 5. Details of normality of curvature and transformations are also given in Appendix 5.

The following steps were taken on examination of the data.

1. To normalise data, the log of results were used for Stroop (colours and reading), Visual Span, CES-D, State-Trait Anxiety Scale and Symptoms. It was discovered that Rey Copy did not show a normal distribution and was not easily transformed into a

normal distribution.

2. On examination the following outliers were removed;
   - one CFS from Stroop tests which fell outside 2 standard distributions from the mean because the patient performed extremely poorly;
   - one CFS from Threshold test that fell outside 2 standard distributions from the mean because the patient performed outstandingly well.

The variance of the different groups was compared. On four tests, CFS patients were significantly worse and *more variable,* (Log (CES-D), Reaction Time Decision and Movement Time, and Finger Tapping) (this was also true for CES-D before the log was taken), and this will need to be borne in mind. Note that the results of looking at data in this way showed that CFS patients' data was more variable than controls. This is consistent with the study's expectations in regard to CFS patients, that is, that some CFS patients will be very much worse at tests and therefore become outliers when compared to others who are partially recovered and will perform normally or near to normal.

Illness and activity data used highly discrete scales (e.g. 0, 1, 2) for which ANOVA was not suitable. Therefore non-parametric analysis was used: the Mann-Whitney test for comparing two groups of data and Kruskal-Wallis for comparing three groups.

### 1.3 Significance

The convention followed in this study is to give two tailed significances which are equal or below 0.1, placing greater weight on those results with higher significance as per Efron and Tibshirani (1993). They rate evidence against the null hypothesis as borderline if $p < 0.1$, the strength of evidence progressively increasing to very strong if $p < 0.01$. Significance levels show either-direction differences. However, for most of this analysis only one direction is being considered. For example, on first testing the alternative hypothesis is only confirmed if CFS patients are worse than controls. Furthermore, using 0.1 significances helps to reveal patterns of performance, since accumulations of 0.1

significances by chance when the null hypothesis is true is unlikely. Given that this study is with small numbers of subjects, 0.1 significance also indicates that these tests are likely to be significant with larger numbers; however, no importance is attached to individual tests where an 0.1 significance has been found.

### 1.4 Missing and excluded data

It was expected that not all subjects would be able to complete all the tests because of illness, because of fatigue or because of lack of time. In addition, questionnaires are not always filled in correctly resulting in missing data. Missing data was ignored, but where data was missing at first testing all subsequent testings were also excluded on that test. Questionnaires where a small number of items were not answered were scored by scaling up the percentage of marks collected.

One patient with dyslexia, whose low NART score was inconsistent with his other test-results, was excluded from the analysis of NART and from the analysis of the other test that involved reading, Stroop. One subject had forgotten her glasses, so was unable to carry out the Threshold and Visual Span tasks; she carried out the Stroop test, but due to obvious difficulty on this test, her data were excluded. In addition, her second-testing result for this test was also excluded, as it might have been affected by practise. Two CFS patients who had absences (asleep or lost consciousness) during the Reaction Time test, and hence extremely slow scores, were considered to have an exceptional problem; their data were excluded from the Reaction-Time analysis.

## 2. Results: Part 1. The subjects: propensity to illness, psychiatric profile and beliefs

What was expected:

1. CFS patients would have higher pre-illness activity, higher contact with CFS related illnesses, and more treatment with antibiotics.

2. CFS patients when ill would have restricted activity compared to control groups.
3. CFS and Crohns/colitis patients would score higher on psychiatric indicators, life events and have more external locus of control.

## 2.1 Subject Profile

### 2.1.1 Predisposition to illness

The general questionnaire, given to all the subjects, produced the following differences between CFS and control groups.

In respect of vulnerability to, or predisposition of a subject to CFS, significant differences (Table 5) were found between the three groups using a non-parametric test (Kruskal-Wallis). These significant differences suggest:-

- CFS subjects had more contact prior to illness with CFS or its associated illnesses (e.g. EBV and Coxsackie B) than control groups.
- CFS subjects thought they had taken more antibiotics in the two years prior to their illness than the control groups.
- CFS subjects had more serious illness prior to the CFS than normal controls in a similar period.
- CFS subjects, prior to their illness, did more social and fitness activity than Crohns/colitis.
- CFS subjects had more life events of a serious nature than Crohns /colitis patients.

**Table 5: Illness and activity data - results of comparisons.**

This Table gives results on illness and activity data. Three groups of subjects are shown (CFS patients, normal controls and Crohns/colitis controls). Results for 9 illness propensity measures and 5 activity measures are shown for each group of subjects. This data was highly discrete, so tests relying on Normality, such as ANOVA, were unsuitable; therefore, a non-parametric tests was used. The Table shows, in each case, the mean for each group, followed by the results of carrying out a Kruskal-Wallis test: the mean rank for each group, the chi-square statistic, and the calculated significance (after the statistic is corrected for ties, carried out automatically by SPSS), with significance levels as shown below. The statistic shows whether there is a difference between the groups in *either* direction. Significant differences between the CFS group and both control groups for "Prior antibiotics", "Contact with trigger" and "problems hoovering & washing and reading & TV"; between the CFS and Normal groups for "Physical activity at work", "Prior serious illness", "Housework" and "Hours in leisure activities outside the home"; and between the CFS and Crohns/colitis groups for "Life events" and "Prior activity". There are no significant differences in the opposite direction to that expected (i.e. the CFS patients performing worse than the control groups).

* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001.

| | means | | | mean ranks | | | chi-square | signi- |
|---|---|---|---|---|---|---|---|---|
| Tests | CFS | Normal | C/c | CFS | Normal | C/c | statistic | cance |
| Illness propensity profile | | | | | | | | |
| Prior antibiotics | 0.48 | 0.03 | 0.06 | 53 | 40 | 41 | 12.46 | p=.002*** |
| Life events | 2.18 | 1.80 | 1.32 | 64 | 56 | 41 | 8.68 | p=.013** |
| Physical activity at work | 1.79 | 1.05 | 1.39 | 66 | 47 | 56 | 7.57 | p=.023** |
| Prior activity (current activity for Normals) | 11.65 | 9.33 | 6.52 | 64 | 53 | 38 | 10.80 | p=.005*** |
| Contact with trigger illness | 1.04 | 0.44 | 0.45 | 68 | 48 | 50 | 11.78 | p=.003*** |
| Prior serious illness | 0.40 | 0.05 | 0.36 | 62 | 47 | 56 | 10.11 | p=.006*** |
| Athletic history | 2.79 | 2.30 | 2.12 | 61 | 55 | 52 | 1.70 | p=.428 |
| Studying | 1.24 | 0.85 | 0.52 | 47 | 56 | 43 | 4.01 | p=.135 |
| Difference in activity after illness | | | | | | | | |
| Housework | 1.77 | 2.30 | 1.89 | 50 | 67 | 54 | 6.51 | p=.039** |
| Problems hoovering and washing | 0.95 | 0.06 | 0.00 | 65 | 37 | 36 | 39.88 | p<.001*** |
| Problems reading and TV | 0.96 | 0.08 | 0.08 | 79 | 40 | 41 | 55.10 | p<.001*** |
| Achievement goals | 0.64 | 0.83 | 0.60 | 54 | 62 | 52 | 2.39 | p=.303 |
| Hours in leisure activity outside the home (now) | 2.80 | 9.33 | 4.41 | 39 | 81 | 52 | 37.63 | p<.001*** |

Subject Profile - Illness Variables

At the time of testing, the questionnaire results showed significant differences on non-parametric (Mann-Whitney) analysis between CFS patients and Crohns/colitis controls on illness variables (Table 6):

- CFS patients were significantly less able than Crohns/colitis patients to "cope" during their illness;
- CFS patients reported significantly longer delay in receiving a diagnosis of their illness than Crohns/colitis patients;
- CFS patients reported a significantly less positive response to the question as to whether doctors were helpful than Crohns/colitis patients;
- CFS patients had significantly shorter length of illness than Crohns/colitis patients.

The delay in diagnosis of CFS patients compared to Crohns/colitis patients and the feeling that doctors were unhelpful may contribute to the lower level of coping that CFS patients seem to experience. CFS patients had had shorter length of illness than Crohns/colitis patients, therefore their lack of ability to cope cannot be due to having a long illness alone.

Table 6. Differences on illness variables between CFS and Crohns/colitis patients

This Table gives results on illness variables. Two groups of subjects are shown (CFS patients, and Crohns/colitis controls) (the variables are not relevant to the normal controls). Results for 6 illness variables are shown for each group of subjects. This data was highly discrete, so tests relying on Normality, such as ANOVA, were unsuitable; therefore, a non-parametric tests was used. The Table shows, in each case, the mean for each group, followed by the results of carrying out a Mann-Whitney test: the mean rank for each group, the test statistic, and the calculated significance (after the statistic is corrected for ties, carried out automatically by SPSS). The statistic shows whether there is a difference between the two groups in *either* direction, with significance levels shown below. Significant differences are found on coping with illness, delayed diagnosis, and length of illness.

* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001.

| Test | means | | mean ranks | | stati- | signifi- |
|---|---|---|---|---|---|---|
| | CFS | C/c | CFS | C/c | stic | cance |
| Coping with illness | 0.62 | 0.88 | 41 | 33 | 2.33 | .020 ** |
| Delayed diagnosis | 1.13 | 0.56 | 39 | 30 | 2.16 | .031 ** |
| Helpful medics | 1.07 | 1.71 | 30 | 43 | 2.84 | .005 *** |
| Expectations | 9.98 | 35.13 | 32 | 39 | 1.41 | .159 |
| Getting better | 0.65 | 0.77 | 35 | 39 | 1.04 | .296 |
| Length of illness | 3.20 | 5.83 | 29 | 39 | 1.96 | .050 ** |

Subject Profile - Activity Level

At the time of testing, the questionnaire results showed significant differences on Kruskal-Wallis analysis between CFS patients during their illness and controls on activity levels (Table 5):

- CFS subjects had more problems reading, hoovering or hanging up washing;
- CFS subjects did significantly less housework than normal controls;
- CFS subjects did significantly fewer activities than normal.

The interaction of fatigue and symptoms was analysed with depression and anxiety, activity levels, and other health questions for CFS patients. Analysis of a number of variables was carried out to see whether CFS patient symptoms, including feelings, were consistently correlated (Table 7). The significant findings showed groupings of correlated variables as follows:-

- Higher fatigue, more symptoms per week, problems with reading, depression, anxiety and less coping were all highly correlated (positively) together. Therefore, more symptoms or problems on one meant more symptoms/problems/fatigue and less coping on the others.
- Difficulty reading correlated (positively) significantly with more fatigue, more symptoms (that week), and more depression and anxiety.
- The answer that doctors were helpful was correlated (positively) significantly with more coping and less fatigue.
- The length of illness correlated (positively) significantly with increased anxiety.
- Delay in diagnosis correlated (positively) with a longer length of illness.
- More symptoms that week correlated highly (positively) with more depression, anxiety and fatigue; these all correlate (positively) , but less strongly, to having problems reading.

These results suggest that symptoms, mood, attitude and activity are very interrelated in CFS. The direction of causality is not shown but these correlations suggest either depression and anxiety are caused by CFS or that CFS symptomatology is caused by

## Table 7. Correlations between illness and psychological variables: page 1 of 2.

The following table shows the correlations between the illness and psychological variables. The correlations are pair-wise, that is, each correlation is calculated using all of the subjects for which data on both variables exist; the number of subjects used for each calculation is shown below each value in brackets, since the correlations are therefore based on different numbers of subjects.

Two-tailed significances

* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001

Further results

Two additional variables were analysed in this part of the study.

(i) The CFS patients were asked whether they were getting better. This had a very poor response, so there was insufficient data for correlations to be meaningful. When correlated with the variables shown on the table, the only significant correlation found was with Trait Anxiety (-.657 (n=10) **).

(ii) The variable "Work" which showed in categories whether the subject worked, was correlated with the none of the variables shown in the table, although it was correlated with the variable described in (i) (-.620 (n=11) **).

**Table 7. Correlations between illness and psychological variables: page 2 of 2.**

| | Log(State Anxiety) | Trait Anxiety | Log(Symptoms that week) | Fatigue | Problems Reading | Length of Illness | Helpful Coping | Time to Diagnosis | medical profession |
|---|---|---|---|---|---|---|---|---|---|
| Log (CES-D) | +.641**** (108) | +.713**** (106) | +.687**** (108) | -.586**** (107) | +.521**** (104) | +.064 (103) | -.304** (63) | +.230* (64) | -.323*** (62) |
| Log(State Anxiety) | | +.732**** (107) | +.481**** (109) | -.389**** (108) | +.463**** (105) | +.194** (103) | -.255** (64) | +.224* (65) | -.197 (63) |
| Trait Anxiety | | | +.545**** (107) | -.487**** (106) | +.434**** (103) | +.214** (101) | -.231* (62) | +.124 (63) | -.167 (61) |
| Log(Symptoms that week) | | | | -.564**** (108) | +.554**** (105) | +.199** (103) | -.330** (64) | +.262** (65) | -.396**** (63) |
| Fatigue | | | | | -.503**** (104) | -.013 (102) | +.319** (63) | -.073 (64) | +.362*** (62) |
| Problems Reading | | | | | | +.163 (101) | -.192 (67) | +.087 (68) | -.223* (66) |
| Length of illness | | | | | | | -.063 (60) | +.252** (62) | +.121 (60) |
| Coping | | | | | | | | -.274** (68) | +.424**** (67) |
| Time to diagnosis | | | | | | | | | -.182 (68) |

depression and anxiety. Doctors attitudes and diagnosis are external factors that may influence recovery since a helpful doctor and early diagnosis seems to correlate with coping and the length of the illness as well as perceived fatigue of patients.

## 2.2 Data Personality, Psychiatry Beliefs and Symptoms

The patients were given a number of questionnaires relating to their psychiatric profile and beliefs. These were the Health Locus of Control (HLOC) scale and Middlesex Health Questionnaire (MHQ) and illness questions. They were completed only once between first and second testing. HLOC and illness questionnaires were used to look at differences in attitude between the groups that might relate to their illness. The MHQ scale gave an indication of psychiatric profile.

The subjects were also given standard self-report questionnaires on depression and anxiety at each testing: the Speilburger Anxiety Scale and the CES-D depression scale. At each testing, they were scored on fatigue and symptoms. Results of the first testing are discussed below. The results of the repeat testing are also discussed with relation to the cognitive tests later.

### 2.2.1 The Middlesex Health Questionnaire

Table 8 shows the differences between the three subject groups on the the MHQ. It shows that the CFS patients are very significantly more Anxious ($p<0.001$), Somatising ($p<0.001$) and Depressed ($p<0.001$) than both control groups, and more Phobic ($p<0.05$) and Obsessional ($p<0.01$) than normal controls. CFS patients also score as more depressed on the CES-D ($p<0.001$) and more anxious on the Spielberger state/trait anxiety Scale ($p<0.001$) than both control groups. No significant differences are found between the normal and Crohns/colitis group. On answering the questionnaire more CFS patients reply that they had depression than both control groups and Crohns/colitis patients significantly more than normal controls.

### 2.2.2 Health Locus of Control

Table 8 shows the differences between the three subject groups on the Health Locus of Control. CFS patients are more likely than both Crohns/colitis and normal controls (the latter difference is not significant) to feel that what happens to them is due to chance. CFS patients show much less belief in powerful others than Crohns/colitis, who may transfer their feelings of loss of control due to illness to believing in doctors.

**Table 8. Psychological questionnaires and mood - results of comparisons**

This Table gives the results from the psychological questionnaires and measures of depression, anxiety and symptoms. Three groups of subjects are shown (CFS patients, normal controls and Crohns/colitis controls). Results are shown for the six measures on the Middlesex Health Questionnaire (MHQ) and the three measures from the Health Locus of Control (HLOC). The Table shows, in each case, the mean and standard deviation for each group, an F-statistic obtained by ANOVA for the differences in performance across groups, and the significance of differences between pairs of groups according to the Scheffe test. No significant differences between CFS and control groups were found in the opposite direction to that expected. As can be seen, significant differences were found between CFS and both control groups on two of the MHQ measures and between CFS and Normal controls on a further two; and significant differences were found between CFS and Crohns/colitis controls on the HLOC Chance and Powerful Others measures.

Two-tailed levels of significance

* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001.

| Test | F-statistic | d.f. | CFS Mean | CFS St.Dev. | CFS v. Normal | Normal Mean | Normal St.Dev. | Normal v.C/c | Crohns/colitis Mean | Crohns/colitis St.Dev. | C/c v. CFS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Middlesex Health Questionnaire | | | | | | | | | | | |
| Anxiety | 13.35 | 2,86 | 8.0 | 3.4 | **** | 6.0 | 3.3 | | 4.8 | 3.5 | *** |
| Phobic | 4.68 | 2,87 | 5.5 | 3.2 | ** | 3.6 | 2.5 | | 4.0 | 1.8 | |
| Obsessional | 7.52 | 2,87 | 7.6 | 3.1 | *** | 4.5 | 2.8 | | 6.1 | 4.3 | |
| Somatic | 23.75 | 2,87 | 7.9 | 3.1 | **** | 3.1 | 2.8 | | 3.9 | 3.4 | **** |
| Depressed | 8.19 | 2,86 | 6.4 | 2.7 | *** | 4.0 | 3.5 | | 3.5 | 2.9 | *** |
| Hysteria | 1.78 | 2,87 | 3.5 | 2.6 | | 4.7 | 3.3 | | 3.5 | 2.9 | |
| Locus of control | | | | | | | | | | | |
| Chance | 4.48 | 2,87 | 20.9 | 5.1 | | 18.9 | 3.6 | | 17.3 | 4.7 | ** |
| Internal | 1.72 | 2,88 | 20.3 | 6.5 | | 23.1 | 5.7 | | 21.3 | 6.3 | |
| Powerful others | 2.72 | 2,87 | 16.6 | 3.4 | | 16.9 | 2.5 | | 18.8 | 4.8 | * |

**Table 8. Psychological questionnaires and mood - results of comparisons: continued**

| Test | | F-statistic | d.f. | CFS Mean | CFS St.Dev. | CFS v. Normal | Normal Mean | Normal St.Dev. | Normal v.C/c | Crohns/colitis Mean | Crohns/colitis St.Dev. | C/c v. CFS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mood | | | | | | | | | | | | |
| Log(CES-D) | (#) | 29.2 | 2,104 | 19.23 | 8.17 | **** | 7.98 | 8.22 | | 6.32 | 5.01 | **** |
| Anxiety: Trait | | 12.5 | 2,104 | 46.28 | 9.43 | **** | 36.05 | 9.21 | | 39.47 | 10.09 | ** |
| Log(State) | (#) | 10.4 | 2,106 | 42.22 | 9.23 | **** | 33.85 | 9.56 | | 36.35 | 8.04 | ** |
| Symptoms: Log(that week) | (#) | 50.8 | 2,106 | 37.93 | 21.92 | **** | 7.63 | 8.26 | | 7.70 | 7.33 | **** |
| Log(now) | (#) | 43.0 | 2,106 | 16.29 | 13.71 | **** | 2.27 | 3.48 | | 2.04 | 3.91 | *** |
| Fatigue | | 22.5 | 2,105 | 3.23 | 1.96 | **** | 6.39 | 2.31 | | 5.57 | 2.56 | **** |

Notes

(#) denotes means of original (not Log) values, given for ease of comparison; the ANOVAs are carried out on Log values.

### 2.2.3 Beliefs about Illness

Table 9 shows the significant differences between the three groups on questions asked about what subjects believed about six different illnesses. Thirty questions were asked in all, those not shown in the Table showing no significant difference; it should be noted that with this number of questions, some spurious significance are likely. On the question of whether people recover from illnesses, CFS patients think that people were less likely to recover from arthritis (this was significantly different from normal controls and outstandingly different from Crohns/colitis patients); Crohns/colitis patients think they were more likely to recover from Multiple Sclerosis (MS) than normal controls and CFS patients but less likely to recover from a broken leg than CFS patients. On the question of whether they believed they have a large chance of getting the illness, normal controls think they have less chance of getting CFS than either CFS patients or Crohns/colitis patients did. CFS patients also think that doctors know more about stomach ulcers than Crohns/colitis patients do. Crohns/colitis patients think that MS scared people less than normal controls and CFS patients do.

### 2.2.4 The CES-D

The CES-D scores show the CFS patients as having significantly higher scores ($p<0.001$) on depression and the difference in average score to be very much higher than both control groups (an average score for CFS patients of 19, compared to 6 and 8 for the Crohns/colitis and normal controls respectively). This is a clear result showing that CFS patients report a far higher level of symptoms of depression than controls.

### 2.2.5 The Spielberger Questionnaire

The Spielberger State/Trait anxiety questionnaire results show the CFS patients scoring way above controls on anxiety scores. The results are significantly different at the $p<0.0001$ level and show an average score of 42 for CFS patients compared to 33-36 for controls (for State Anxiety; similarly for Trait Anxiety). This is a very clear difference showing CFS patients as scoring very highly compared to controls on Spielberger's anxiety questionnaire.

## Table 9. Illness Beliefs questionnaire - results of comparisons

This Table gives the results from the Illness Beliefs questionnaire. Three groups of subjects are shown (CFS patients, normal controls and Crohns/colitis controls). Results are given for the six of the 30 Illness Beliefs questionnaire for which significant differences were found. The Table shows, in each case, the mean and standard deviation for each group, an F-statistic obtained by ANOVA for the differences in performance across groups, and the significance of differences between pairs of groups according to the Scheffe test. The Scheffe test tests the null hypothesis that group means are equal.
Two-tailed significances:

* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001.

| Question (high score indicates agreement with the statement) | F-statistic | d.f. | CFS Mean | CFS St.Dev. | CFS v. Normal | Normal Mean | Normal St.Dev. | Normal v.C/c | Crohns/colitis Mean | Crohns/colitis St.Dev. | C/c v. CFS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Low prospects of recovery from arthritis | 9.24 | 2,83 | 6.3 | 1.0 | ** | 5.3 | 1.7 | | 4.6 | 1.7 | **** |
| Low prospects of recovery from Multiple Sclerosis | 6.75 | 2,83 | 6.7 | 0.6 | | 6.4 | 1.0 | * | 5.6 | 1.6 | *** |
| Many peope get ME/CFS/PVFS | 5.20 | 2,83 | 4.4 | 1.5 | ** | 3.3 | 1.4 | * | 4.4 | 1.7 | |
| Multiple Sclerosis scares people | 4.83 | 2,83 | 6.6 | 0.9 | | 6.5 | 0.7 | ** | 5.6 | 1.7 | ** |
| Stomach ulcers are badly understood by doctors | 3.77 | 2,84 | 1.7 | 0.8 | | 2.1 | 1.3 | | 2.6 | 1.6 | ** |
| Low prospects of recovery from a broken leg | 3.76 | 2,83 | 1.2 | 0.9 | | 1.5 | 1.6 | | 2.3 | 1.9 | ** |

### 2.2.6 Fatigue and Symptoms

CFS patients rated their level of fatigue (on a line) and number of symptoms (from a list) both 'that week' and 'now' significantly more highly than controls ($p<0.0001$). The differences were large, with a symptom rating for CFS patients of 37 on average 'that week' compared to around 7 on average from both groups of controls. On the fatigue line CFS patients on average placed their mark 3 centimetres (out of 10) nearer the exhausted level than controls.

### 2.2.7 Summary

The CFS patients had more scores suggesting psychiatric tendencies on the MHQ (para 2.2.1) than controls, and, contrary to expectations, the Crohns/colitis group did not score significantly higher than normal controls on these tests (Table 8).

The CFS patients were more depressed (significantly and at much higher levels) according to the CES-D scale. The CFS patients were more anxious (significantly and at much higher levels) according to the scores on the Spielberger anxiety questionnaire. CFS patients had beliefs about illness which were more external in their locus of control. CFS patients had significantly, and much higher levels of reported symptoms and fatigue. Crohns/colitis patients excluded for testing because they were 'upset' at a consultant's appointment may mean this group's depression scores were lower than they are in that population.

Correlations within the CFS group showed that anxiety and depression were strongly related to symptoms fatigue and problems with reading. Fatigue also correlated with coping.

Results suggest very high levels of depression and anxiety in CFS patients; these scores are related to fatigue and symptoms.

## 3 Results: Part 2. Cognitive test battery and mood

What was expected:-

(a) CFS patients will be worse on a number of cognitive tests compared to matched controls.

(b) CFS patients' performance will improve as they recover, significantly more than the control group.

(c) Crohns/colitis controls will perform as normal controls on some tests but will perform as CFS patients where tests are affected by factors relating to chronic illness.

(d) The differences between normal controls and CFS patients may be partly accounted for by depression and /or anxiety.

### 3.1 Results: First Cognitive Testing

The three subject groups were compared at first testing to see whether there were any differences between them; in particular to see whether CFS patients scored worse on some of these tests.

Table 10 shows the results of comparing the scores of CFS, Crohns/colitis patients and normal controls on the set of cognitive tests at first testing using an ANOVA.

Weighting data

A number of the memory tests and word fluency tests used different versions. This use of different versions is commonly used in clinical testing but always involves the problem of the interchangeability of the tests (Golden et al. 1990). To overcome this the test results have been examined and corrected to allow for any difference whch could significantly affect results. The procedure was as follows:

1) Check that the distribution of versions throughout the groups was not biased by being significantly uneven. Significant differences were not found in the proportion of each

Table 10 Differences between CFS, Normal controls and Crohns/colitis controls at 1st testing: page 1 of 2

This Table gives the results from the 1st testing session. Three groups of subjects are shown (CFS patients, normal controls and Crohns/colitis controls). Results for 19 measures taken from 14 cognitive tests and 6 measures taken from 4 questionnaires of symptoms and mood are given for each group of subjects. The Table shows, in each case, the mean and standard deviation for each group, an F-statistic obtained by ANOVA for the differences in performance across groups, and the significance of differences between pairs of groups according to the Scheffe test. As can be seen, significant differences are found on 11 of the 14 cognitive tests and all of the symptoms and mood questionnaires. The most significant differences between CFS and controls are on psychomotor tests and measures of symptoms and mood.

Two-tailed levels of significance:
* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001.

| Test | F-statistic | d.f. | CFS Mean | CFS St.Dev. | CFS v. Normal | Normal Mean | Normal St.Dev. | Normal v.C/c | C/c Mean | C/c St.Dev. | C/c v. CFS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Memory Tasks | | | | | | | | | | | |
| (i) Language | | | | | | | | | | | |
| Logical memory (Z-score)(1) | 2.93 p=.0577 | 2,106 | -0.25 | (1.09) | * | 0.25 | (0.91) | | 0.12 | (0.91) | |
| Associate learning | 3.87 p=.0238 | 2,104 | 14.02 | (3.80) | | 15.51 | (3.25) | ** | 13.09 | (3.47) | |
| Word recognition: Correct | 4.20 p=.0178 | 2,98 | 8.40 | (2.35) | ** | 9.79 | (2.13) | | 8.86 | (1.83) | |
| Correct - Errors | 3.38 p=.0378 | 2,104 | 7.16 | (2.85) | ** | 8.63 | (2.56) | | 7.91 | (2.09) | |
| (ii) Other | | | | | | | | | | | |
| Digit forward + digit back | 0.50 p=.6065 | 2,106 | 11.93 | (1.95) | | 11.61 | (2.01) | | 12.09 | (2.02) | |
| Rey memory (Z-score)(1) | 8.39 p=.0004 | 2,97 | -0.27 | (1.09) | *** | 0.51 | (0.87) | *** | -0.44 | (0.97) | |
| Rey copy | 1.09 p=.3399 | 2,104 | 35.09 | (1.26) | | 35.39 | (0.92) | | 34.76 | (2.90) | |
| Log(Visual span) (#) | 1.57 p=.2123 | 2,105 | 12.51 | (4.02) | | 11.22 | (4.18) | | 11.27 | (3.64) | |
| Tasks requiring speed | | | | | | | | | | | |
| (i) Language | | | | | | | | | | | |
| Stroop: Log(Reading) (#) | 11.4 p<.0001 | 2,98 | 39.18 | (9.09) | *** | 33.60 | (6.13) | | 30.91 | (4.62) | **** |
| Log(Colours) (#) | 2.73 p=.0709 | 2,82 | 80.48 | (14.29) | | 74.69 | (13.67) | | 71.43 | (13.25) | * |
| Word fluency (per min.) | | | | | | | | | | | |
| Hard letter (Z-score)(1) | 0.62 p=.5420 | 2,104 | -0.10 | (0.98) | | 0.12 | (1.02) | | -0.11 | (0.97) | |
| Categories (Z-score)(1) | 2.93 p=.0577 | 2,104 | -0.22 | (1.15) | * | 0.30 | (0.95) | | -0.16 | (0.84) | |

Table 10 Differences between CFS, Normal controls and Crohns/colitis patients at 1st testing: page 2 of 2

| Test | F-statistic | d.f. | CFS Mean | CFS St.Dev. | CFS v. Normal | Normal Mean | Normal St.Dev. | Normal v.C/c | C/c Mean | C/c St.Dev. | C/c v. CFS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (ii) Other | | | | | | | | | | | |
| Reaction time (milliseconds) | | | | | | | | | | | |
| Decision time | 21.8 p<.0001 | 2,103 | 365.68 | (65.24) | **** | 306.46 | (22.82) | | 305.86 | (23.35) | **** |
| Movement time | 10.3 p=.0001 | 2,105 | 283.53 | (76.83) | **** | 226.85 | (33.61) | | 248.08 | (48.46) | * |
| Finger Tapping (per min.) | 12.8 p<.0001 | 2,77 | 287.20 | (68.97) | **** | 353.21 | (30.99) | | 334.05 | (55.82) | ** |
| WAIS Digit Symbol (raw) | 14.3 p<.0001 | 2,105 | 49.39 | (12.70) | **** | 63.14 | (10.52) | | 59.39 | (13.71) | *** |
| Threshold task (score) | 4.00 p=.0215 | 2,96 | 2.09 | (0.59) | ** | 1.75 | (0.66) | | 1.73 | (0.47) | * |
| PASAT (out of 60) | 1.37 p=.2611 | 2,82 | 31.63 | (14.11) | | 33.35 | (13.37) | | 40.50 | (15.18) | |
| Visual spatial task | | | | | | | | | | | |
| WAIS blocks (raw score) | 0.01 p=.9894 | 2,80 | 38.08 | (7.16) | | 37.83 | (7.54) | | 37.72 | (10.72) | |
| Mood | | | | | | | | | | | |
| Log(CES-D) (#) | 29.2 p<.0001 | 2,104 | 19.23 | (8.17) | **** | 7.98 | (8.22) | | 6.32 | (5.01) | **** |
| Anxiety: Trait | 12.5 p<.0001 | 2,104 | 46.28 | (9.43) | **** | 36.05 | (9.21) | | 39.47 | (10.09) | ** |
| Log(State) (#) | 10.4 p=.0001 | 2,106 | 42.22 | (9.23) | **** | 33.85 | (9.56) | | 36.35 | (8.04) | ** |
| Symptoms: Log(that week) (#) | 50.8 p<.0001 | 2,106 | 37.93 | (21.92) | **** | 7.63 | (8.26) | | 7.70 | (7.33) | **** |
| Log(now) (#) | 43.0 p<.0001 | 2,106 | 16.29 | (13.71) | **** | 2.27 | (3.48) | | 2.04 | (3.91) | *** |
| Fatigue | 22.5 p<.0001 | 2,105 | 3.23 | (1.96) | **** | 6.39 | (2.31) | | 5.57 | (2.56) | **** |

Notes

(#) denotes means of original (not Log) values, given for ease of comparison; the ANOVAs are carried out on Log values.

(1) Z-scores are corrected for test-version used, as described in Appendix 4 Table 3(e). The overall means and standard deviations for the whole sample are as follows:

| | mean | st.dev. |
|---|---|---|
| Logical memory | 10.11 | (3.75) |
| Word fluency: hard letter | 8.22 | (4.16) |
| Word fluency: categories | 17.87 | (4.45) |
| Rey memory | 22.74 | (7.41) |

group doing a particular version although distributions were not exactly the same. While every attempt was made to distribute the test versions evenly at first testing this could not apply to second testing where the person did an alternative version.

2) Check that means of different versions were not significantly different. Differences were found between versions on the word fluency test, the Logical Memory test and Rey Memory test.

3) On these tests (in 2 above) the results were adjusted by the z score of the version used, adjusted for the distribution of the population doing each version (see Appendix 4). The use of z scores for weighting data is a standard procedure (Lyman 1963).

(For details of weighting see Appendix 4).

### 3.1.1 Memory tests

The scores of all groups are quite high on the memory tests, reflecting their higher level of IQ. For example, group means for the normal group show them as slightly higher than the norms given for age 30-39 year olds by Hulika 1966 (Associate Learning 15.48 (sd 3.48) Logical Memory 7.99 (Form 1)(sd 2.95)) and for adults by Osterrieth (1944) (Rey Complex: Figure copy 32, memory 22); and CFS patients score above the norm for Logical memory and within one standard deviation of the Associate Learning Score.

CFS patients do significantly worse than normal controls on several of the memory tests. The CFS group perform significantly worse than the normal control group on Rey Memory ($p<0.01$) and Word Recognition ($p<0.05$) and the Logical Memory test is significantly worse at the 0.1 level of significance. The CFS Associate Learning score is lower than in the normal group but only significantly different between normal and Crohns/colitis patients.

The differences between CFS patients and normal controls on these memory tests are not reproduced between CFS patients and Crohns/colitis patients. The Crohns/colitis patients' Associate Learning Score, Word Recognition score and Rey Complex Figure

memory scores are closer to that of the CFS group than the normal group. Because the Crohns/colitis patients are performing as badly as the CFS group there is no significant difference between CFS and Crohns/colitis patients on Word recognition and on Rey Memory; the Crohns/colitis group are significantly worse than the normal group on Rey Memory and Associate learning and on some tests they are worse than CFS patients.

It is noticeable that neither the CFS or the Crohns/colitis group do worse on the Digit Span and the Visual Span test. This may be because these tests require immediate/short term rather then longer term memory.

### 3.1.2 Psychomotor, vigilance and language speed tests.

The CFS patients score very significantly differently ($p<0.001$) from normal controls on reaction time movement and decision time and on finger tapping. These tests are tests of speed; they show CFS patients as very markedly different in speed of decision and movement. The CFS patients are also poorer on the on the WAIS Digit Symbol task ($p<0.001$) and the Threshold task ($p<0.05$). These tests involve vigilance, fast information processing and psychomotor skills. On all these tests the same differences are found between CFS and Crohns/colitis patients which suggests that this is a robust difference and peculiar to the CFS group.

The CFS patients score significantly worse ($p<0.01$) on the less difficult part of the Stroop test, ie reading the text in different coloured ink, but much less significantly worse on the harder part. CFS patients also score worse, but only at 0.1 level, on the category word fluency task.

### 3.1.3 The Groups compared over the whole cognitive battery

The overall results show CFS patients scoring less well than normal controls on 90% of the tests at their first attempt, the differences being significant on over half of the tests.

As expected, no significant differences are found where CFS patients are better than controls; this increases the real significance of the results. One can conclude that CFS patients are performing less well on cognitive tests than one would expect given their age and IQ. However the Crohns/colitis patients score poorer on memory tests compared to normal controls, suggesting that these differences are not specific to CFS. The reaction time tasks and vigilance task tests on the other hand are very slow compared to the normal controls, particularly for some individuals; our outliers (950 ms) would be regarded as very abnormal. Differences on Reaction time, Stroop Reading, Digit Symbol and Finger Tapping are very significant and are not shared by the Crohns/colitis group. Therefore these tests are more likely to be an indicator of CFS. These are all tasks that involve speed of both information processing (or vigilance) and muscle control i.e. movement, articulation or writing.

### 3.1.4 Fatigue during the Reaction Time test

The reaction time test (as discussed Method 5.3.5) was repeated to see if CFS patients had an abnormal amount of fatigue and are slower by the end of the reaction time test instead of improving due to practise. The results of subtracting the second set of movements from the first set of movements was analysed using a t-test. The result in Table 11 shows that the CFS subjects are significantly different from normal controls on change during the Reaction Time test.

On decision time normal controls get faster ($p<0.05$) but CFS patients get slower (this is also true with regard to Crohns/colitis patients). On movement time all the groups get slower but CFS patients get slower still ($p<0.05$) than normal controls. This confirms that CFS patients are actually getting slower during testing and that they may be fatiguing very quickly. The slowing could also be due to motivational factors.

**Table 11. Slowing During Testing: Differences between CFS, Normal Controls and Crohns/Colitis Patients at First Testing.**

This Table gives results on Reaction Time (both Decision Time and Movement Time measures) from the 1st testing session. To show the effect of slowing during testing, the Reaction Time measured over the second set of 40 test movements was subtracted from that measured over the first set of 80 test movements. Results are shown for three groups of subjects (CFS patients, normal controls and Crohns/colitis controls). The Table shows the mean and standard deviation for each group. Also shown is the result of a t-test carried out between the CFS group and the normal control group, correcting for unequal variances; because of lack of data from the third group, the Crohns/colitis patients group was not included in the analysis.

Two-tailed significance ** = p<0.05

| | CFS | | Normal | | CFS v. normal | Crohns/colitis | |
|---|---|---|---|---|---|---|---|
| Test (millisecs) | mean | s.d. | mean | s.d. | t-test | mean | s.d. |
| Decision Time | -1.76 | 35.96 | 14.11 | 22.78 | t(53.28)=2.17 ** | 11.50 | 15.13 |
| Movement Time | -16.09 | 38.53 | -0.50 | 17.28 | t(44.66)=2.17 ** | -4.30 | 17.81 |

(the two t-statistics are the same).

### 3.1.5 Specific problems in the memory tests

Looking at tests individually, specific problems could have been occurring for CFS patients on particular memory tests. The differences in scoring of the Rey Complex figure are generally due to CFS patients recalling less items, but some CFS patients fail to see the rectangle as one unit and built up the figure by compartment; however since those who do so were less than 10% of patients it might be that they have a particular problem and nothing general can be concluded from the observation. This effect is not observed in subjects in the other groups.

In the Logical memory task, CFS patients seemed to show good recall of the first part of the passage, and poor recall for the last part of the passage. On analysing the first 5 and the last 5 scoring segments of the Logical Memory task, the following results are found:

| | score for first five marks | | score for the last five marks | |
|---|---|---|---|---|
| | Mean | St.Dev. | Mean | St.Dev. |
| CFS | 2.94 | 1.01 | 1.10 | 1.37 |
| Normals | 3.25 | 0.92 | 1.87 | 1.58. |

Both groups remember less at the end of the passages, but while CFS patients are not significantly different at remembering the beginning of the passage (a Mann-Whitney test statistic of 1.48, p=0.140), they are significantly worse at remembering the end of the passage (a Mann-Whitney test statistic of 2.44, p=0.015).

### 3.1.6 Specific test problems in language tasks

In the word recognition task subjects were scored according to how many items they marked and separately on how accurately they recalled the words, and they were penalised for errors. It is found by looking at the number of words guessed (i.e. correct and incorrect) that at second testing there is a tendency, by both groups, to guess more

words but CFS subjects are more accurate when they do so.

Summary 3.1.7

CFS patients perform less well on psychomotor tasks at first testing. The evidence found of slowing down of CFS subjects during reaction time tasks (compared to controls) suggests that there may be a fatiguing process in CFS. Memory tests are also done better by normal controls than the other groups but this also is true when normals are compared to the Crohns/colitis group.

## 3.2 Results: Changes in performance between first and second testing

### 3.2.1 Choosing the analysis for comparing the results at first and second testing.

The analysis of first and second testing was done comparing CFS and normal controls. The Crohns/colitis data were not included in this analysis but results are shown, for interest, in graph form in Appendix 6. The Crohns/colitis data was not included because:

- the Crohns/colitis group data at first testing have already shown the information most pertinent to the analysis of the three groups;
- the analysis of all three groups at first and second testing on an ANOVA produces a complicated set of interactions that are difficult to disentangle to be sure what they mean;
- the Crohns/colitis control group was smaller to start, with 23; with retesting drop-out numbers fell to 17 and thus below the level where significant differences are likely to be found between first and second testing.

The Graphs in Appendix 6 show the improvement of Crohns/colitis patients compared to that of other groups. It is highly noticeable that Crohns/colitis patients rather than CFS or normal controls are most often the group showing least improvement. It is possible that the Crohns/colitis group learn less well for reasons that are peculiar to that group.

### 3.2.2 Comparisons between CFS and normal groups on first and second testing.

Analysis of first and second testing was required to compare improvements between the CFS and control groups. Analysis was executed using a mixed model Analysis Of Variance (ANOVA) with repeated measures to take into account 1) between-subjects factor and 2) within subjects factors. This type of analysis would distinguish differences caused by group differences, repetition or the interaction between these two.

This shows three effects:-

1) the difference between first and second testing i.e. improvement or decline in performance, for the whole sample; this is the REPETITION EFFECT;
2) the overall difference between the groups, taking into account both before and after scores; this is the GROUP EFFECT;
3) the interaction between 1) and 2), showing the difference in the change in performance between the groups i.e. whether the two groups improve in performance differently; this is the INTERACTION EFFECT.

Performance improvement between first and second testing is only of interest if it is greater in the CFS group. If it is the same in both groups this is probably due to practise. Table 12 shows the means of the cognitive tests on the first and second testing (for subjects for which two testings were available), F-statistics and significance of the differences. Note that the data used are only those of the people who completed the requisite test at both testings; means shown for the first testing on this Table may therefore not be the same as those shown for the first testing on Table 10.

The Graphs in Appendix 6 show the differential improvement for each group at first and second testing and CFS patients who completed three testings (the figures from which these graphs are drawn are also given in Appendix 6).

## Table 12 Contrast in Improvement: page 1 of 3

This Table gives the results on differences between the 1st and 2nd testing sessions. Two groups of subjects are shown (CFS patients and normal controls). Results for 19 measures from 14 cognitive tests and 6 measures from 4 questionnaires of symptoms and mood are given for each group of subjects. The Table shows, in each case, the mean and standard deviation for each testing session for each group, followed by the results of ANOVAs: the results given are the significance of the Repetition effect (i.e. which test-occasion), Group effect (i.e. the subject group) and the interaction between these two effects. Note that only subjects who performed both tests are included, so means given here are not the same as Table 10. As can be seen, significant group differences when both testings are taken into account are found on Stroop Reading, Word Fluency Categories, both Reaction Time measures, Finger Tapping, WAIS Digit Symbol and all mood and symptom measures; in all cases, CFS are worse than controls, as expected. The interaction is significant for Associate Learning, Word Recognition (Correct), Stroop Colours, Reaction Time Movement Time, WAIS Digit Symbol and Symptoms That Week, showing that the performance of CFS patients is improving above that of normal controls.
Two-tailed significances:
* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001

| | CFS | | | | | Normal | | | | | F-values | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test | 1st mean | (s.d.) | 2nd mean | (s.d.) | N | 1st mean | (s.d.) | 2nd mean | (s.d.) | N | d.f. | Repetition | Group | Interaction |
| Memory Tasks | | | | | | | | | | | | | | |
| (i) Language | | | | | | | | | | | | | | |
| Logical memory (Z-score)(1) | -0.13 | (1.10) | 0.30 | (0.77) | 37 | 0.08 | (0.98) | 0.37 | (0.99) | 23 | 1,58 | 5.87 p=.019** | 0.48 p=.49 | 0.21 p=.647 |
| Associate learning | 14.52 | (3.10) | 14.81 | (3.62) | 34 | 15.91 | (3.73) | 14.04 | (3.86) | 23 | 1,55 | 3.23 p=.078* | 0.14 p=.711 | 6.09 p=.017** |
| Word recognition: Correct | 8.51 | (2.29) | 9.77 | (2.39) | 35 | 9.77 | (1.97) | 9.68 | (2.20) | 22 | 1,55 | 2.83 p=.098* | 1.35 p=.251 | 3.79 p=.057* |
| Correct - Errors | 7.29 | (2.91) | 7.78 | (2.98) | 36 | 8.83 | (2.73) | 8.00 | (2.72) | 24 | 1,58 | 0.13 p=.721 | 2.25 p=.139 | 2.06 p=.157 |
| (ii) Other | | | | | | | | | | | | | | |
| Digit forward + digit back | 11.89 | (1.91) | 12.30 | (1.87) | 37 | 11.87 | (2.18) | 12.46 | (1.88) | 23 | 1,58 | 5.22 p=.026** | 0.01 p=.903 | 0.14 p=.708 |
| Rey memory (Z-score)(1) | -0.16 | (1.12) | 0.24 | (1.02) | 36 | 0.18 | (0.90) | 0.52 | (0.91) | 19 | 1,53 | 9.69 p=.003*** | 1.40 p=.243 | 0.06 p=.813 |

**Table 12 Contrast in Improvement: page 2 of 3**

| Test | CFS 1st mean | CFS (s.d.) | CFS 2nd mean | CFS (s.d.) | CFS N | Normal 1st mean | Normal (s.d.) | Normal 2nd mean | Normal (s.d.) | Normal N | d.f. | F-values Repetition | F-values Group | F-values Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rey copy | 34.97 | (1.32) | 35.03 | (1.71) | 37 | 35.46 | (0.80) | 34.77 | (1.38) | 22 | 1,57 | 1.86<br>p=.178 | 0.15<br>p=.703 | 2.56<br>p=.115 |
| Log(Visual span) (#) | 13.00 | (4.03) | 12.40 | (4.19) | 37 | 10.73 | (3.97) | 11.55 | (3.08) | 22 | 1,57 | 0.00<br>p=.969 | 1.82<br>p=.183 | 1.91<br>p=.173 |
| Tasks requiring speed | | | | | | | | | | | | | | |
| (i) Language | | | | | | | | | | | | | | |
| Stroop: Log(Reading) (#) | 39.25 | (9.34) | 38.47 | (12.63) | 32 | 32.57 | (4.19) | 32.78 | (4.52) | 23 | 1,53 | 0.44<br>p=.509 | 8.00<br>p=.007*** | 0.83<br>p= .366 |
| Log(Colours) (#) | 80.78 | (15.40) | 76.89 | (19.55) | 18 | 73.32 | (13.73) | 77.00 | (19.81) | 22 | 1,38 | 0.28<br>p=.602 | 0.55<br>p=.461 | 5.91<br>p=.020** |
| Word fluency (per min.) | | | | | | | | | | | | | | |
| Hard letter (Z-score)(1) | -0.01 | (1.00) | 0.31 | (0.94) | 37 | 0.33 | (1.02) | 0.49 | (0.93) | 21 | 1,56 | 1.97<br>p=.166 | 1.62<br>p=.209 | 0.26<br>p=.609 |
| Categories (Z-score)(1) | -0.18 | (1.19) | 0.08 | (1.36) | 36 | 0.32 | (0.97) | 0.42 | (0.82) | 21 | 1,55 | 0.79<br>p=.377 | 2.93<br>p=.092* | 0.15<br>p=.696 |
| (ii) Other | | | | | | | | | | | | | | |
| Reaction time (milliseconds) | | | | | | | | | | | | | | |
| Decision time | 356.4 | (62.26) | 341.9 | (69.18) | 35 | 309.5 | (26.64) | 298.0 | (27.84) | 21 | 1,54 | 3.65<br>p=.061* | 11.30<br>p=.001*** | 0.05<br>p=.827 |
| Movement time | 277.9 | (77.77) | 256.5 | (67.21) | 36 | 231.6 | (31.14) | 230.5 | (32.18) | 22 | 1,56 | 3.47<br>p=.068* | 5.60<br>p=.021** | 2.83<br>p=.098* |
| Finger Tapping (per min.) | 287.5 | (77.73) | 332.1 | (48.03) | 17 | 358.1 | (30.90) | 376.0 | (31.47) | 19 | 1,34 | 9.46<br>p=.004*** | 18.96<br>p<.001**** | 1.72<br>p=.198 |
| WAIS Digit Symbol (raw) | 49.94 | (12.44) | 57.29 | (10.44) | 35 | 62.09 | (8.39) | 63.04 | (11.85) | 23 | 1,56 | 10.42<br>p=.002*** | 11.29<br>p=.001*** | 6.17<br>p=.016** |
| Threshold task (score) | 2.09 | (0.60) | 1.89 | (0.56) | 31 | 1.85 | (0.65) | 1.83 | (0.47) | 22 | 1,51 | 2.17<br>p=.147 | 1.16<br>p=.287 | 1.49<br>p=.228 |
| PASAT (out of 60) | 32.88 | (14.50) | 39.31 | (13.17) | 32 | 33.10 | (12.25) | 42.43 | (11.30) | 21 | 1,51 | 25.71<br>p<.001**** | 0.25<br>p=.618 | 0.87<br>p=.356 |

**Table 12: Contrast in improvement: page 3 of 3**

| Test | | CFS 1st mean | CFS (s.d.) | CFS 2nd mean | CFS (s.d.) | CFS N | Normal 1st mean | Normal (s.d.) | Normal 2nd mean | Normal (s.d.) | Normal N | d.f. | F-values Repetition | F-values Group | F-values Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visual spatial task | | | | | | | | | | | | | | | |
| WAIS blocks (raw score) | | 37.39 | (6.93) | 40.17 | (7.72) | 23 | 36.76 | (6.67) | 39.43 | (6.78) | 21 | 1,42 | 12.48 p=.001*** | 0.12 p=.731 | 0.01 p=.940 |
| Mood | | | | | | | | | | | | | | | |
| Log(CES-D) | (#) | 19.03 | (7.47) | 18.06 | (9.44) | 36 | 6.29 | (5.42) | 5.14 | (5.94) | 21 | 1,55 | 5.11 p=.028** | 56.38 P<.001**** | 0.87 P=.356 |
| Anxiety: Trait | | 46.56 | (10.11) | 43.21 | (11.10) | 34 | 33.65 | (9.10) | 32.95 | (7.10) | 20 | 1,52 | 3.63 p=.062* | 20.69 p<.001**** | 1.56 p=.218 |
| Log(State) | (#) | 42.32 | (9.85) | 40.08 | (11.96) | 37 | 32.85 | (8.15) | 31.20 | (7.32) | 20 | 1,55 | 4.66 p=.035** | 14.69 p<.001**** | 0.11 p=.740 |
| Symptoms: Log(that week) | (#) | 37.76 | (22.44) | 28.22 | (16.36) | 37 | 5.57 | (6.37) | 6.81 | (9.74) | 21 | 1,56 | 0.25 p=.621 | 83.75 p<.001**** | 3.25 p=.077* |
| Log(now) | (#) | 15.76 | (11.96) | 12.35 | (12.42) | 37 | 1.91 | (3.86) | 3.00 | (7.33) | 21 | 1,56 | 0.85 p=.360 | 68.17 p<.001**** | 1.01 p=.318 |
| Fatigue | | 3.25 | (1.99) | 4.19 | (2.16) | 36 | 6.25 | (2.61) | 6.80 | (2.02) | 20 | 1,54 | 4.47 p=.039** | 32.47 p<.001**** | 0.31 p=.579 |

Notes

(#) denotes that means of original (not Log) values are given for ease of comparison; the ANOVAs are carried out on Log values

(1) Z-scores are corrected for test-version used, as described in Appendix 4. The overall means and standard deviations for the whole sample are as follows:

| | mean | st.dev. |
|---|---|---|
| Logical memory | 10.11 | 3.75 |
| Word fluency: hard letter | 8.22 | 4.16 |
| Word fluency: categories | 17.87 | 4.45 |
| Rey memory | 22.74 | 7.41 |

Results of comparisons

The results show the effect of repetition is significant on Logical Memory (p=0.019), Digit span (p=0.026), Rey Complex Figure (Memory, p=0.003), PASAT (p<0.001) and WAIS Block Design (p=0.001) There are no other important effects on these particular tests, so while both groups improve on these tests there is no significant difference between groups in their improvement. These are therefore likely to be straightforward practise effects. The graphs confirm this pattern of similar improvement in CFS patients but Crohns/colitis patients did not improve on some of these tests. It seems from this and other results that Crohns/colitis patients show less practise and learning effects and that this may be related to their condition: it is possible that either the effect of malabsorption or the drugs used to treat Crohns/colitis depress the ability of the subject to benefit from practise and new learning.

The results show a CFS group effect on Stroop Reading (p=0.007) and word fluency categories (p=0.092 only); neither group improves significantly but CFS patients are worse, to the same degree, on both testings. This suggests CFS patients have a poorer performance on these tests which are stable and does not respond to recovery in the short term. Appendix 6 Graph 9 shows CFS patients catching up with controls over three testings on Stroop reading and suggests recovery is taking place on the Stroop reading. Graphs 3 and 4 show word recognition figures to be fluctuating. The results show an effect of repetition and an interaction of both effects on Word Recognition and Associate Learning. On Word Recognition this is because CFS performance improves while normals stay the same. On Associate Learning this is because Normals get worse while CFS stay the same; in this test, negative practise effects may cause worsening performance, probably due to the order in which test version were given . However in the case of CFS patients, recovery may offset the effect of negative practise.

An interaction effect only is found on Stroop Colours (p=0.020) here CFS are improving but normals get worse at the test. This suggests either that CFS patients are recovering

on a test where practise is a disadvantage or that, on this test, the results are not very reliable on re-test.

There is a repetition and group effect on Reaction Time Decision Time ($p=0.061$ and $p=0.001$ respectively) and Finger Tapping ($p=0.004$ and $p<0.001$ respectively). This is because the CFS group are worse in these tests at first testing but improve at second testing at a similar rate to normal controls, therefore, improvement seems to be due to practise. The CFS group stay very significantly worse on these tests. The Graphs for reaction time decision time show uniform downward (quicker) reaction time. The finger tapping graph shows similar improvement in CFS and normal control groups, with differences becoming slightly smaller. The Crohns/colitis group again make no improvement. This lack of improvement in the Crohns/colitis group is characteristic of their results and suggests a problem in this control group that should be further investigated with reference to those conditions.

All three comparisons (repetition, group and interaction) occur in Reaction Time Movement Time ($p=0.068$, 0.021 and 0.098 respectively) and WAIS Digit Symbol ($p=0.002$, 0.001 and 0.016 respectively) because the CFS patients start much worse than normal controls, then improve at the second testing, although still not performing as well as the normal controls. This suggests that some improvement may be due to repetition and some to recovery. Appendix 6 Graphs 14 and 16 show Crohns/colitis patients improving similarly to CFS patients although still maintaining a group difference compared to the normal group who make no improvement.

Summary

At second testing the differences between the CFS patients and the normal controls are consistent and are shown, over both testings, on Stroop reading, on word fluency categories (but only at the 0.1 level), reaction time, finger tapping, and WAIS digit symbol.

Graphs of the three subject groups

The graphs in Appendix 6 showing the three groups at first and second testing give additional information with which to evaluate the differences between the groups. Looking at these graphs confirms that some differences between testings are probably due to the instability of the measure and others due to a real difference between the CFS and other groups. For example, the WAIS Digit Symbol task, shows similar improvement for the control groups but far greater improvement for the CFS group; however, when the graphs for Reaction time (movement time) is seen, the Crohns/colitis group looks as though it is making similar improvement to the CFS group. Differences on Visual Span, when the three groups are seen together look as though any differences are due to retest variability.

Illness variables - change over time

As discussed in the Method chapter, CFS patients have significant large differences in the number and severity of symptoms and in perceived fatigue from both controls. These group differences occur when both testings are analysed not just at first testing. At second testing fatigue is reduced for both CFS and normal groups and reporting of symptoms "now" improved in CFS patients slightly more than controls. By second testing CFS measures of illness have improved overall. One must take into account that an improvement of the scale from 3 to 4 (almost exhausted to near 1/2 activity level) may represent a larger change than from 7 to 8 (representing slightly below normal to normal scores). Appendix 6 Graphs 20-25 show the change between first and second testing for all three groups. However, change in depression and anxiety are not significantly different between CFS and normals and therefore are unlikely to account for improvements in cognitive performance in CFS patients.

### 3.2.3 Trends for CFS patients at third testing

The graphs in Appendix 6 show the means of CFS patients on the cognitive tests over three testings, for the patients who were tested three times. They allow us to see the

trend of test scores. It shows for example that in Threshold, Reaction time (movement) and Finger Tapping tests CFS patients maintain the improvement made at second testing but do not in word recognition and word fluency. CFS patients continue to improve at third testing on Logical Memory, Reaction Time, decision and movement time, finger tapping, and Stroop colours and reading. The means at third testing are shown in Appendix 6. Unfortunately not enough controls repeated testing a third time for statistical analysis to be appropriate.

Summary of results of repeat testing

A group effect on psychomotor tasks such as Reaction Time (DT), and Finger Tapping tests continues to show CFS patients scoring below normal controls.

This is also true of language tasks such as Stroop colours and word fluency (category).

On Reaction Time (MT) and Digit Symbol the CFS patient's scores show some gain on the lead of the normal controls (but Reaction Time (MT) improvement is also seen to be similar in the graphs showing Crohns/colitis patients). The effects of practise can be seen in the repetition effect and complicates the meaning of the scores.

## 3.4 Depression and anxiety

### 3.4.1 Depression scoring at first testing

Two main measures of mood were taken at the time of each testing: the Spielberger state/trait anxiety scale and the CES-D depression scale. At the first testing, CFS patients had very significantly higher levels of anxiety on both state and trait scales and depression scores than both normal controls and Crohns/colitis patients.

### 3.4.2 Depression scoring at second testing

Depression scores and anxiety improve slightly in both groups, but CFS patients do not improve more than normals. The group differences at second testing remain highly

significant. CFS patients still score extremely highly on all measures of depression and anxiety and on symptoms and fatigue. The improvement of CFS patients on mood could effect recovery, but the improvement is only a small proportion of the difference between CFS patients and normal controls.

### 3.4.3 Results of looking at depression scores as a covariate

#### Cognition and Mood correlated

The changes seen in cognition could be due to an improvement in mood not to a general remission in the illness. The previous paragraph however shows that there is no CFS group improvement, in mood, above normal controls between first and second testing; however individuals may improve on both mood and test performance. The relationship between depression scores and cognitive performance is examined in this section. Firstly the relationship between the tests results for all groups are correlated to depression scores at first testing.

The results of the correlations, shown in Table 13, show mood is highly correlated with most of the tests where highly significant differences are found between CFS and normal controls. These are the psychomoter tests - Reaction Time (Decision Time), Finger Tapping and Digit Symbol - and Word Fluency and Stroop. These correlations need to be treated with caution because the results so far tell us that the depression score for the CFS patients is much higher than for controls so that any effect that is associated with CFS will for this reason correlate with depression scores.

**Table 13: Correlations between cognitive tests and mood variables: page 1 of 2**

This Table shows correlations between cognitive test results and mood variables, considering all of the subjects in the study together. Results for 19 measures from 14 cognitive tests were taken, and their Pearson correlation with 3 measures of mood calculated, the three mood measures being Log(CES-D depression rating), Trait anxiety and Log(State anxiety). For each cognitive measure, for each measure of mood, firstly the Pearson correlation is shown, then the significance, then the number of subjects on which that correlation is based; the correlations are pair-wise, that is, each correlation is calculated using all of the subjects for which data on both variables exist. As can be seen, significant correlations with mood are found for both Rey measures, Visual Span, both Stroop measures, both Word Fluency measures, both Reaction Time measures, Finger Tapping, Wais Digit Symbol and PASAT. There are no significant correlations in the opposite direction to that expected.

Two-tailed significances
* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001

**Table 13: Correlations between cognitive tests and mood variables at first testing: page 2 of 2**

| Test | Correlations with Log(Depression) | | | Correlations with Trait Anxiety | | | Correlations with Log(State Anxiety) | | |
|---|---|---|---|---|---|---|---|---|---|
| Memory Tasks | Corr | Sig. | n | Corr | Sig. | n | Corr | Sig. | n |
| (i) Language | | | | | | | | | |
| Logical memory (Z-score) | -.12 | .23 | 107 | -.02 | .82 | 107 | -.15 | .11 | 109 |
| Associate learning | -.04 | .70 | 105 | .05 | .63 | 106 | .07 | .51 | 107 |
| Word recognition: Correct | -.16 | .10 | 99 | -.10 | .30 | 100 | -.05 | .61 | 101 |
| Correct - Errors | -.09 | .39 | 105 | .03 | .79 | 105 | .04 | .71 | 107 |
| (ii) Other | | | | | | | | | |
| Digit forward + digit back | -.07 | .46 | 107 | -.11 | .28 | 107 | -.07 | .47 | 109 |
| Rey memory (Z-score) | -.07 | .48 | 99 | -.11 | .28 | 98 | -.26 | .01*** | 100 |
| Rey copy | .02 | .80 | 105 | -.10 | .32 | 105 | -.19 | .05** | 107 |
| Log(Visual span) | .20 | .04** | 105 | .11 | .28 | 105 | -.01 | .88 | 107 |
| Tasks requiring speed | | | | | | | | | |
| (i) Language | | | | | | | | | |
| Stroop: Log(Reading) | .39 | <.001**** | 99 | .41 | <.001**** | 100 | .35 | <.001**** | 101 |
| Log(Colours) | .27 | .01** | 83 | .17 | .11 | 85 | .12 | .28 | 85 |
| Word fluency (per min.) | | | | | | | | | |
| Hard letter (Z-score) | -.14 | .15 | 105 | -.13 | .18 | 105 | -.16 | .09* | 107 |
| Categories (Z-score) | .18 | .06* | 105 | -.24 | .01** | 105 | -.19 | .05* | 107 |
| (ii) Other | | | | | | | | | |
| Reaction time (milliseconds) | | | | | | | | | |
| Decision time | .45 | <.001**** | 103 | .28 | <.005*** | 103 | .28 | <.005*** | 105 |
| Movement time | .19 | .05* | 106 | .16 | .11 | 106 | .16 | .09* | 108 |
| Finger Tapping (per min.) | -.34 | <.005*** | 79 | -.27 | .02** | 79 | -.34 | <.005*** | 80 |
| WAIS Digit Symbol (raw) | -.23 | .02** | 105 | -.11 | .27 | 105 | -.12 | .22 | 107 |
| Threshold task (score) | .00 | .94 | 96 | .05 | .65 | 97 | -.06 | .56 | 98 |
| PASAT (out of 60) | -.16 | .16 | 84 | -.19 | .08* | 84 | -.22 | .04** | 85 |
| Visual spatial task | | | | | | | | | |
| WAIS blocks (raw score) | .01 | .92 | 82 | .00 | .99 | 82 | -.09 | .43 | 83 |

If the results of the CFS patients and normal subjects are analysed separately then differences that arise just because CFS patients score poorly on both a test and depression score are eliminated. Table 14 below shows these results. There are no correlations between the normals test results and depression at below the 0.05 level of significance (and only one below the 0.1 level). CFS results also correlate mildly with Digit Span and PASAT, which are performed well by the CFS patients. CFS patients' poor performance on the Stroop is highly correlated with depression score as is word fluency. On psychomotor tasks, depression score is highly correlated to Reaction Time (Decision). This is a strange set of results showing, as it does, mildly significant correlations between tests and depression score on tests where the effect of this does not lead to below normal scores; and the results fail to show correlations with Reaction Time (Movement), Digit Symbol, and Rey Memory where CFS show very significant differences from normal subjects. One can conclude that depression score is not the only factor in differences on CFS performance. In order to tease out the effect of depression from other effects, e.g. CFS illness, an ANCOVA was used to apportion the effect of depression (as shown by depressed score) on the significance of differences at first testing.

**Table 14: Correlations between cognitive tests and depression within subject groups at first testing: page 1 of 2**

This Table shows correlations between cognitive test results and depression (log(C-DES), considering only CFS subjects, then only normal subjects. Results for 19 measures from 14 cognitive tests were taken. For each cognitive measure, firstly the Pearson correlation is shown, then the significance, then the number of subjects on which that correlation is based; the correlations are pair-wise, that is, each correlation is calculated using all of the subjects for which data on both variables exist. As can be seen that performance is correlated with depression within the CFS groups for Digit forward + back, Stroop (both tests), Word Fluency (both tests), Reaction Time Decision TIme and PASAT. For the Normal group, performance and depression are correlated only or Finger Tapping.

Two-tailed significances
* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001

**Table 14: Correlations between cognitive tests and depression within subject groups at first testing : page 2 of 2**

| Test | Correlations with Log(CDES) CFS subjects Corr | Sig. | n | Normal subjects Corr | Sig. | n |
|---|---|---|---|---|---|---|
| Memory Tasks | | | | | | |
| (i) Language | | | | | | |
| Logical memory (Z-score) | .08 | .61 | 45 | -.09 | .56 | 41 |
| Associate learning | .17 | .28 | 43 | -.07 | .65 | 41 |
| Word recognition: Correct | -.06 | .73 | 40 | -.05 | .77 | 39 |
| Correct - Errors | -.10 | .50 | 43 | .12 | .44 | 41 |
| (ii) Other | | | | | | |
| Digit forward + digit back | -.26 | .09* | 45 | -.16 | .31 | 41 |
| Rey memory (Z-score) | -.01 | .95 | 43 | .10 | .55 | 38 |
| Rey copy | -.14 | .37 | 45 | -.03 | .84 | 41 |
| Log(Visual span) | -.03 | .85 | 44 | .19 | .24 | 41 |
| Tasks requiring speed | | | | | | |
| (i) Language | | | | | | |
| Stroop: Log(Reading) | .42 | .01*** | 38 | .17 | .29 | 40 |
| Log(Colours) | .46 | .03** | 23 | .16 | .33 | 39 |
| Word fluency (per min.) | | | | | | |
| Hard letter (Z-score) | -.43 | <.005*** | 45 | -.16 | .34 | 39 |
| Categories (Z-score) | -.29 | .05* | 45 | -.15 | .37 | 39 |
| (ii) Other | | | | | | |
| Reaction time (milliseconds) | | | | | | |
| Decision time | .44 | <.005*** | 43 | .07 | .66 | 39 |
| Movement time | .19 | .21 | 45 | -.14 | .40 | 40 |
| Finger Tapping (per min.) | -.33 | .11 | 25 | -.29 | .08* | 38 |
| WAIS Digit Symbol (raw) | -.15 | .33 | 43 | .00 | .99 | 41 |
| Threshold task (score) | .12 | .49 | 37 | -.25 | .12 | 40 |
| PASAT (out of 60) | -.34 | .03** | 40 | .01 | .96 | 37 |
| Visual spatial task | | | | | | |
| WAIS blocks (raw score) | -.13 | .47 | 35 | .00 | .98 | 37 |

In order to judge the strength of relationships between cognitive tests and depression score in our CFS group and to see if depression can account for the differences between CFS and the normal group, the data was analysed in the following way. An ANCOVA was carried out, an extension of ANOVA in which the effects are assessed after scores are adjusted for differences associated with a covariate. The ANCOVA gives an F value to show the importance of depression in accounting for differences in test performance. Table 15 below shows the results of the ANCOVA using scores from the CFS and normal control groups, and using depression as a covariate. Table 15 includes a comparison of the group deviations from the mean, both unadjusted and after adjustment, for the covariate.

It was found that the use of an additional, second covariate (anxiety) made little difference to the results, and therefore was unnecessary, according to the statistical principle of parsimony. This was not surprising, since depression score was found to be highly correlated with both State Anxiety (correlation 0.628 (n=108), $p<0.001$) and Trait Anxiety (correlation 0.737 (n=106), $p<0.001$).

The CES-D scores were used as the co-variate in their raw state. Since the commonly used covariates are non-normal distributions, such as age and demographic characteristics (see Tabachnick and Fichell 1989 p23 and 317), transformation of this data would be unnecessary and might lead to a less linear relationship between depression and the test measures. The depression score CES-D meets the requirement (Tabachnick and Fichell 1989 p. 319) to be a continuous variable related to the dependent variable.

The effects of type of group are shown to be accounted for by depression (as shown by depression score) on Stroop and Word Fluency (scores on these tests are also shown to be correlated with depression score for CFS patients in Table 14). Depression score is shown to be related to reaction time and finger tapping and Digit Symbol scores but not to affect significantly the group differences on those tests. Significant effects remain

**Table 15. Differences on cognitive tests (at first testing) between subject groups when depression is used as a covariate: page 1 of 3**

This Table gives the results from the 1st testing session, when account is taken of depression. Results for 19 measures taken from 14 cognitive tests and 3 measures of mood and symptoms are shown for two groups of subjects (CFS patients and normal controls). ANCOVAs were carried out on the results from each measure, using depression (CES-D) as a covariate. The Table shows the F-statistics obtained for the covariate and for the group difference, and also the degrees of freedom for the statistic and their significance. Also given are the grand mean for each mean, the mean deviation for each group (unadjusted), and the mean deviation for each group when adjusted for the covariate.
The covariate alone can be seen to be significant for both Stroop measures, both Word Fluency measures and PASAT. The group effect alone can be seen to be significant for Logical Memory, Word Recognition (Correct-Errors), Digit Span. Both covariate and group effect can be seen to be significant for Word Recognition (Correct), Rey Memory, both Reaction Time measures, Finger Tapping, WAIS Digit Symbol, both Symptom measures and Fatigue.

Two-tailed significances.

* p<0.1 ** p<0.05 *** p<0.01 **** p<0.001.

| Test | F-values: Covariate | F-values: Group | d.f. | Grand mean | Unadjusted mean deviations CFS | Unadjusted mean deviations normal | Adjusted mean deviations CFS | Adjusted mean deviations normal |
|---|---|---|---|---|---|---|---|---|
| **Memory Tasks** | | | | | | | | |
| (i) Language | | | | | | | | |
| Logical memory (Z-score)(1) | 1.528 p=.220 | 3.749 p=.056* | 1,83 | -0.011 | -0.24 | 0.26 | -0.24 | 0.27 |
| Associate learning | 1.193 p=.278 | 2.472 p=.120 | 1,81 | 14.75 | -0.73 | 0.76 | -0.71 | 0.74 |
| Word recognition: Correct | 4.049 p=.048** | 3.625 p=.061* | 1,76 | 9.09 | -0.69 | 0.71 | -0.61 | 0.63 |
| Correct - Errors | 1.178 p=.281 | 5.08 p=.028** | 1,81 | 7.88 | -0.72 | 0.75 | -0.77 | 0.81 |
| (ii) Other | | | | | | | | |
| Digit forward + digit back | 2.636 p=.108 | 3.948 p=.050** | 1,83 | 11.78 | 0.15 | -0.17 | 0.47 | -0.51 |

Table 15. Differences on cognitive tests (at first testing) between subject groups when depression is used as a covariate: page 2 of 3

| Test | F-values Covariate | Group | d.f. | Grand mean | Unadjusted mean deviations CFS | normal | Adjusted mean deviations CFS | normal |
|---|---|---|---|---|---|---|---|---|
| Rey memory (Z-score)(1) | 3.352 p=.071* | 8.743 p=.004*** | 1,78 | 0.096 | -0.36 | 0.41 | -0.38 | 0.43 |
| Rey copy | 1.106 p=.296 | 0.655 p=.421 | 1,83 | 35.23 | -0.14 | 0.16 | -0.11 | 0.12 |
| Log(Visual span) (#) | 0.522 p=.472 | 2.044 p=.15 | 1,82 | 11.17 | 1.07 | 0.93 | 1.07 | 0.93 |
| Tasks requiring speed | | | | | | | | |
| (i) Language | | | | | | | | |
| Stroop: Log(Reading) (#) | 25.69 p<.001**** | 0.953 p=.332 | 1,75 | 35.48 | 1.07 | 0.93 | 1.02 | 0.99 |
| Log(Colours) (#) | 5.79 p=.019** | 0.259 p=.613 | 1,59 | 75.7 | 1.05 | 0.98 | 1.02 | 1.00 |
| Word fluency (per min.) | | | | | | | | |
| Hard letter (Z-score) | 8.67 p=.004*** | 0.417 p=.52 | 1,81 | 0.004 | -0.10 | 0.12 | 0.07 | -0.09 |
| Categories (Z-score) | 9.31 p=.003*** | 0.538 p=.465 | 1,81 | 0.022 | -0.24 | 0.27 | -0.09 | 0.11 |
| (ii) Other | | | | | | | | |
| Reaction time (milliseconds) | | | | | | | | |
| Decision time | 26.32 p<.001**** | 10.42 p=.002*** | 1,79 | 336 | 26.8 | -29.5 | 18.7 | -20.6 |
| Movement time | 7.37 p=.008*** | 11.28 p=.001**** | 1,82 | 256.9 | 26.7 | -30.0 | 24.8 | -27.9 |
| Finger Tapping (per min.) | 19.8 p<.001**** | 11.6 p=.001**** | 1,60 | 327.0 | -39.8 | 26.2 | -30.6 | 20.2 |
| WAIS Digit Symbol (raw) | 12.3 p=.001**** | 15.9 p<.001**** | 1,81 | 56.3 | -6.50 | 6.81 | -5.89 | 6.18 |

**Table 15. Differences on cognitive tests (at first testing) between subject groups when depression is used as a covariate: page 3 of 3**

| Test | F-values: Covariate | F-values: Group | d.f. | Grand mean | Unadjusted mean deviations: CFS | Unadjusted mean deviations: normal | Adjusted mean deviations: CFS | Adjusted mean deviations: normal |
|---|---|---|---|---|---|---|---|---|
| Threshold task (score) | 1.067 p=.305 | 4.291 p=.042 | 1,74 | 1.91 | 0.17 | -0.16 | 0.18 | -0.17 |
| PASAT (out of 60) | 3.654 p=.060* | 0.858 p=.357 | 1,74 | 32.5 | -0.83 | 0.90 | 1.82 | -1.96 |
| Visual spatial task | | | | | | | | |
| WAIS blocks (raw score) | 0.380 p=.539 | 0.516 p=.475 | 1,69 | 37.9 | 0.11 | -0.11 | 0.86 | -0.81 |
| Mood | | | | | | | | |
| Symptoms: Log(that week) (#) | 114.4 p<.001**** | 37.2 p<.001**** | 1,83 | 14.8 | 2.24 | 0.41 | 1.70 | 0.55 |
| Log(now) (#) | 70.61 p<.001**** | 24.53 p<.001**** | 1,83 | 7.41 | 2.19 | 0.42 | 1.70 | 0.56 |
| Fatigue | 58.07 p<.001**** | 16.11 p<.001**** | 1,82 | 4.75 | -1.53 | 1.64 | -0.97 | 1.04 |

Notes

(#) denotes that the ANOVAs were carried out on Log values; mean deviations have been converted back to the original units, for ease of comparison (and are thus multiplicative factors); similarly, for ease of reading, the anti-log of the grand mean has been shown, which is in the original units (although it should be noted that this is not the same as the original mean).

(1) Z-scores are corrected for test-version used, as described in Appendix 4 Table 3(e). The overall means and standard deviations for the whole sample are as follows:

| | mean | st.dev. |
|---|---|---|
| Logical memory | 10.11 | (3.75) |
| Word fluency: hard letter | 8.22 | (4.16) |
| Word fluency: categories | 17.87 | (4.45) |
| Rey memory | 22.74 | (7.41) |

on Logical Memory, Rey Memory, Reaction Time Movement Time, Reaction Time Decision Time, Digit Symbol and Word Recognition, showing that some other factor besides depression is likely to be at work.

A clear pattern emerges :-

1) On memory tasks: on Rey Memory and Word Recognition (correct-errors), using depression score as a covariate, the differences between normal and CFS groups remain.
2) On language tasks: differences on Stroop and Word Fluency are shown to be accountable by depression (as insdicated by depression score).
3) On psychomotor tasks: these have large differences which were only partially reduced when depression score is used as a covariate.

## 4. Summary of Results

CFS patients are worse overall on first testing on cognitive tests. They improve on a number of the tests, above the improvement of both control groups, at second testing. CFS patients have poorer memory performance than normal controls but so do the Crohns/colitis group. CFS patients are very slow on psychomotor tasks compared to both normal and Crohns/colitis groups; these differences are largely maintained at second testing despite improvement of the CFS group. CFS patients are more depressed, anxious and have adverse psychiatric profile, and taking mood as a covariate accounts for part of the differences in results; significant differences remain. The main differences between CFS and controls are on psychomotor tasks and these, although sensitive to depression, remain extremely significant even after depression is regressed out. Reaction time tests, Finger Tapping, Digit Symbol and Rey Memory tests where CFS patients performed worse than controls remained the most sensitive to group differences throughout the analysis.

# CHAPTER 5. DISCUSSION

## 1 Discussion of method

### 1.1 The CFS group as representing the CFS population

#### 1.1.1 Diagnosis

The problem of uncertain diagnosis has been highlighted in the literature survey. The Holmes CFS diagnosis has been criticised by some as too narrow (i.e. excluding too many), but by others as too open (see the "Criteria" section of the "Literature survey" chapter). The CFS diagnosis is wide enough to suffer from the possibility that different specialists and researchers are working with differing populations. Abbey and Garfinkel (1990) suggest 4 distinct groups of CFS patients varying from strong evidence of organic etiology to strong evidence of psychopathological origin. The patients' treatment is guided by the most prominent symptom or by the beliefs of the G.P. and specialist. The study described in this thesis uses clear diagnostic criteria, nevertheless how representative the subject group is must be affected: by geographic location (CFS is associated with different factors in different areas); by type of source (using Infectious Diseases outpatients) and by attitudes of G.P.'s in the area.

Within the group of CFS patients in this study there are patients with evidence of encephalitic illness (2 in our group showing these cases are not typical), and those whose initial illness was no more than mild flu, included together under the same diagnosis as part of the studied group. Patients from epidemic type outbreaks of CFS as in Glasgow College, where contact and environmental factors seem to play a part, are included with individuals with no pre-illness contact with CFS and where psychological components may be more important (see Table 2G; 38% of CFS patients had no known contact with a trigger illness). Some patients have by their own report made considerable recovery before they are seen. The problems with this mixture of patients are that:-

a) Results of cognitive tests may be underestimated because some patients are not as ill as most, or over-estimated if some patients have other undiscovered conditions (discussion of diagnostic criteria shows that CFS symptoms overlap with many other conditions; in their early stages other conditions may not be detectable by any criteria).

b) Recovery may be under-estimated, because some patients are already considerably improved at first testing.

c) Psychiatric indicators may be over-estimated, because some of the group should be classified as depressed rather than CFS, or under-estimated, because patients with previous psychiatric histories or those on antidepressants are excluded.

The diagnosis used in the study fits in with that being used at the time but more precision in the diagnosis of CFS would make results of studies more reliable. However, it is best to use a recognised basis for criteria rather than more stringent but very different criteria. In our study group it is possible that a minority of the group have more severe, more organically based, illness and others have psychologically induced illness, and it is, therefore, possible that mixing these two groups together confuses the results. However the distribution of results suggests that, although individuals amongst the CFS group are outliers on particular tests, and CFS results are more variable, clear groupings do not occur; results are not bi-modal. Moreover, the high extent of psychiatric indicators throughout the group suggests that psychiatric problems are not just confined to a small minority.

This study's results suggest that psychomotor and memory problems may be a widespread feature of CFS, because the results show so many tests to be significantly lower in performance in a moderately ill CFS group (who are attending an out-patient clinic rather than sick at home) and not just a severely ill group (which literature records, e.g. outbreaks at the Royal Free (Crowley et al. 1957) and at Lake Tao (Buchwald et al.1992); this suggests that the groups are not discrete but are all part of the same syndrome.

### 1.1.2 Subject group compared to its whole population: possible bias in the group

Use of a secondary referral centre.

Sharpe et al. (1991) point out that there is a risk of bias in recruiting from secondary referral centres. This is because the G.P. is selecting whom to send to the referral centre and different G.P.'s will have different knowledge and criteria for that selection, the rules of which are hidden. This means that CFS patients used in this study may be selected by G.P.'s as more organically, rather than psychologically, impaired, and may be only a small percentage of those patients with CFS who consult G.P.'s. (However, as pointed out earlier, psychiatric questionnaire scores are so high in the CFS groups that this is unlikely to be the case.) Therefore our sample might be different from the whole CFS group, e.g. they may be more seriously ill, more persistent patients, or less, or more, psychologically upset. The problem in using more primary sources is that recruiting from primary sources also has disadvantages: diagnosis is more unsure, other illnesses may not have been ruled out and contacts with patients may be more difficult. Community based studies (Lloyd et al. 1990(a); Price et al. 1992; Ho Yen, 1988) suggest the incidence of CFS in the populations is more demographically widespread than in hospital based studies, i.e. CFS affects more male and lower class people than seen in hospital based studies. Middle class, articulate patients may be more likely to be referred to a consultant. Price et al. (1992) have taken populations direct from a community and not through health care at all, but this would be too ill-defined a group for this study.

Subject self-selection

All the subjects agreed to come to the location to take part. In the case of patients, for practical reasons that tended to mean the less ill took part. Since CFS patients found coming to hospital tiring they tended to cancel if they felt particularly unwell; this meant that patients were normally not seen when most ill. The few patients who did come for a session when having a severe relapse did appear to have poor results, e.g. one of the patients in relapse had absences and a median Reaction Time of 900 millisecs. plus. The

acutely ill were therefore, with some exceptions, excluding themselves from the study.

Patterns of retesting

The pattern of attendance for retest was different from first testing. Apart from those who had moved away, the two main reasons for not returning were: firstly, that patients were better and had returned to work so they did not want to take time off (at least 3), and secondly, that they thought the tests too demanding in effort or time (at least 2). The most stated reason for postponement of an appointment was relapse. In one case for example the patient postponed appointments every few months until two years had elapsed between first and second appointments. In about half the CFS patients at least one appointment was postponed. This means that 1) tests do not show decline due to severe relapse, 2) we have perhaps failed to test those who might have shown the most improvement in cognitive testing because of greater or speedier recovery, and 3) retest intervals were greater in the CFS group.

## 1.2 The exclusion criteria discussed

For the type of neuropsychological tests used, it is well known that depression and antidepressants, anti-convulsants, substance abuse, head injury and epilepsy can significantly affect outcome (Wittenborn 1990; Wechsler 1987 p.81-87; Wilson et al.1988; Gillham et al.1988). Age cohorts also differ in performance (Wechsler 1955). Our exclusion criteria were dictated by that evidence. However, in respect of studies on CFS in general, the problem of only selecting part of the population profile is a serious methodological problem. There is now a growing realisation that 'to tease out multifactorial aetiologies will not be aided by excluding the psychiatrically ill from samples of CFS,' Lewis and Wessely (1992) (p95), 'we conclude that the approach of excluding people with physical and psychiatric conditions is first impractical, second premature, especially since the causes of many psychiatric disorders remains obscure, and finally at odds with the common epidemiological approach that assumes a multifactorial aetiology.' The experience of this study backs up this statement: excluding those with

depression is extremely difficult and probably attacks the premise that a representative part of the population is being studied. Those being treated for major depression or suffering from major depression as judged by the consultant and patients records, those with prior psychiatric history or those on antidepressants, were not included in the study, but those who did not come into these groups but still were depressed may have been included, and this study has looked at how depression, as indicated by depression score on a cognitive based scale , might interact with the symptoms. In a future study of this kind the only one of these groups I would exclude are those actually on antidepressants, so as to get a picture of the whole population. However, I would screen, carefully, by structured interview to check these depressed patients were actually suffering from CFS rather than a psychiatric illness, and would want to see the effect depression has on results. Another method to get round this problem with neuropsychological testing would be to use depressed patients as controls in future studies.

## 1.3 The effects of subject selection on results

### 1.3.1 CFS patients

The criteria used were designed to exclude patients with other illnesses. In other studies the inclusion of subjects with other physical illness (for example a case of MS) may lead to the conclusion that more abnormalities exist within the CFS group.

The exclusion of some patients due to past psychiatric history or treatment with antidepressants may lead this study to underestimate the presence of psychiatric symptoms in the CFS group. However the MHQ, depression and anxiety questionnaires show quite clearly that psychiatric indicators are much higher in CFS patients even when patients with psychiatric history, or taking antidepressants, are excluded. In excluding those with psychiatric history and those taking antidepressants the study shows that psychiatric indicators in CFS are not just confined to a small part of the population.

The inclusion of CFS patients with or without any particular viral history may mean that the results found reflect a more diverse neurological profile than if one had used more homogenous CFS patients e.g. a group mostly with high Coxsackie titres (Hamblin et al. 1983; Calder and Warnock 1984). However Kilfedder (1988) shows that the Coxsackie group do not really differ from a general ME group and the justification for dividing patients in this way is now considered suspect (Denman 1990). This sort of division does tend to occur if the subjects of the study are from one epidemic.

It is likely that our CFS patients were different in some ways from the whole population of CFS patients; they may have been of higher average IQ and education for example and they are obviously less ill than some patient groups used, such as those in Bastien's study. However, data from other studies, e.g. Salit (1985) and Stricklin et al.(1990), of severe and less severe CFS patients suggest that the group used in the study is typical of samples from hospital and G.P.s' patients. The results shown are consistent with the majority of studies of CFS (see Section 5) although showing more difference in CFS patients than some and less than others. There is unlikely, therefore, to be a bias in the CFS group causing the finding of spurious results. If anything, the voluntary exclusion of more severely ill patients and of more psychiatrically ill patients would be likely to cause an underestimation of differences between the groups.

### 1.3.2 Crohns/ colitis group

Moderately depressed subjects or those with high current depressed symptamamtology in this group may have been under-represented because the consultant did not think they were suitable for testing or because, as patients with a diagnosed disorder, they were more likely to receive treatment for depression (this was suggested by discussion with Crohns/colitis patients). However, even had the group included more depressed patients, the incidence of high depressed score in CFS patients was so high that it seems unlikely that the results would have been significantly altered.

### 1.3.3 Normal controls

This group were matched for the characteristics of the CFS group. Being members of St. Andrew's Ambulance, they were enthusiastic, above average IQ, more athletic, more likely to volunteer and had more of the younger age group. They were a reasonable match for CFS patients but they were not typical of the whole spectrum of a normal population and should not be considered as such. Their performance would be higher than average due to factors such as IQ and conscientious effort.

### 1.3.4 All groups.

The subjects were all volunteers and could leave at any time; the tasks were quite demanding of time and energy. Therefore, those who completed the task were possibly the most committed, altruistic and able.

### 1.3.5 IQ in CFS

There was no significant difference between groups on IQ but CFS subjects did have a have slightly higher average IQ. All three groups had higher than average IQ and consequently performed well above average on tests of cognition. The NART was used as an indicator of IQ, but according to Bastien (1992) IQ may be very depressed in CFS and even NART performance may deteriorate to a certain extent if IQ is severely affected. Therefore CFS patients could have a slightly higher pre-morbid IQ than is recorded in this study, which would mean that differences shown are understated because the CFS patients should have performed better to be consistent with a higher IQ.

## 1.4 Summary of population profile

The population of the CFS group was influenced by the diagnosis used, the use of a secondary referral centre and the subjects' self selection. These factors may mean the CFS patients in this group were different from a population sample of people with CFS symptoms e.g. more female and more middle class; however the group seemed comparable to groups in other studies. Self selection of patients may mean CFS patients were those least ill at an outpatients clinic. The use of diagnostic and exclusion criteria makes it clear the selection that has been made to compare with future studies. Exclusion of depressed patients on antidepressants was necessary because of effects on the tests used, but some Crohns/colitis patients who were upset at their consultant's appointment were not for ethical reasons passed on for testing and might have been mildly depressed, and CFS patients with unrecognised depression (and therefore not recorded in their medical notes as having present or past psychiatric disorder) could have been included because there would have been no grounds to exclude them in the entry criteria.

## 1.5 Problems of a longitudinal design

Although studying CFS patients over time is very useful in understanding the neuropsychological problems of CFS, a longitudinal design and repeat testing has certain problems:

1. The number of subjects who come back for retesting are, in most studies smaller than the original sample, thus reducing the sample for analysis, and may be different in some way from the original group.
2. Retesting of subjects may be delayed, particularly with an out-patient group. This means that time between test and retest may vary between groups. (Patients frequently cancelled sessions due to relapse and so were probably not seen at their worst nor strictly at 4 month intervals.)
3. Tests have to be suitable for retesting, or it is necessary to use different versions

and take this into account, and practise and repetition effects must be taken into account.

## 1.6 Problems in the measurement of depression in the study

This study used a measure of current symptomatology, the CES-D, to indicate depression in the groups. This means that this measure cannot be said to define those with major depressive disorder or those whose depressed mood qualifies as 'clinical' depression. If such a measure had been used then the results would have shown different categories of depression in the groups, i.e. how many in each group were clinically depressed; it would not necessarily however have given an ordinal measure of depression that would register with all the groups and so could be used statistically for comparing between groups and against other scores.

The assumption in using the CES-D is that on a cognitively based scale, depressive scores represent an indication of underlying depression, since long term depressive symptomatology of this kind forms a large part of the diagnosis of depression. The MHQ measure has been shown to distinguish depressive disorder and is used clinically as a more diagnostic test.

The CES-D questionnaire was chosen as a non-somatic measure of depression, stable even when subjects have an illness where symptoms overlap with depression (Foelker and Shewchuk, 1992). Although the CES-D is not a diagnostic test for major depressive disorder, new work shows that it is highly reliable in distinguishing those people who have clinical depression on the DSM III (Somervell et al. 1993). It seems likely then that unless CES-D patients produce artificially high scores on the CES-D (which we have tried to avoid by using a non-somatic based scale), CFS patients have high depressive symptomatology which in those with scores above 16 are likely to indicate clinical depression.

The literature survey (section 3.1) indicates the high number of studies which suggest clinical depression in CFS patients (Taerke et al. 1981; Katon et al. 1991; Manu et al.1988). Although some contest that CFS patients are clinically depressed (Petersen et al. 1991) the evidence is for high levels of depression, prior psychiatric history and previous depression in CFS patients. Therefore although high CES-D scores in this study do not prove CFS patients have clinical levels of depression they strongly support this view, particularly as in this study CFS subjects also score higher on the MHQ depression scale.

Underlying depression is more relevant to the effect of depression on cognition than depressed score, but depressed scores enable a finer grading of depression for all groups than using a diagnostic test. That this study used a depression score not a diagnosis should be borne in mind; however it seems unlikely that underlying depression is failing to be suitably scored in this measure.

# 2 Discussion of Results Part 1: psychiatric and illness variables

## 2.1 Illness and vulnerability to illness variables

### 2.1.1 Previous health and activity

The results show the CFS patients to be, prior to their illness, significantly more socially and physically active than Crohns/colitis patients. They have more likelihood of having been seriously ill prior to their illness, and remembered being prescribed more antibiotics prior to their illness and having experienced more life events than Crohns/colitis patients. These factors suggest that the CFS patient may actually be vulnerable to CFS due to greater activity and due to greater contact and experience of illness.

There are a number of possible explanations for CFS patients having had more serious illness in the time period before their illness. It could be that serious illness makes one

vulnerable to getting CFS; or that serious illness affects the psychology of individuals so that they are more prone to CFS. Alternatively, it could be that sick patients are more likely to remember past illnesses.

CFS patients according to the results do significantly less activity when ill than the Crohns/colitis patients and they experience difficulty at particular tasks i.e. reading and housework tasks. This could be an indication of the effect of CFS, since CFS patients' general activity level is higher than Crohns/colitis controls pre-illness.

### 2.1.2 Illness ratings in the groups

CFS patients report significantly more symptoms and fatigue than Crohns/colitis patients. The rate at which symptoms are recorded, some as high as 70 points, indicates the range of symptoms CFS patients experience. These excessively high scores suggest that the CFS patients may be very sensitised to 'picking up' symptoms; they report a wide spectrum of symptoms. They do not report only those symptoms which are most distressing while disregarding symptoms of lesser nuisance, which alternative behaviour would suggest more illness and less sensitivity to symptoms. CFS patients seem to complain about a wide range of symptoms irrespective of their relative importance. The drop in symptoms at later testing may represent a de-sensitising to symptoms rather than recovery (see section 2.4.1). The fatigue level of patients is, however, supported in the results by the performance of CFS patients, which shows slowing down during the reaction time task. The Threshold task and finger tapping task results also suggest CFS patients are suffering from fatigue.

## 2.2 Psychiatric Profile and beliefs

As might be expected from the literature, the CFS patients as a group clearly had far more psychiatric problems than the controls, though whether this was a cause of CFS or is a result of it is not shown in these results. However, the scores at second testing

of depression and anxiety show little improvement over time despite other recovery and suggests that the depression (as indicated by depressed score) is not the sole cause of these problems, although mood may just be very slow to reco

### 2.2.1 Depression in the medically ill

Rodin et al. (1986) discuss depression in the medically ill and state that there is often a joint cause of illness and depression. The evidence of pituitary, thyroid, endocrine, viral and neurological complications in an illness is associated with depression. CFS has, as shown in the literature survey, been associated with all of these, as well as with chronic pain which is also associated with depression. Moreover the problems of sense of loss of identity, of job and career are also associated with depression. If CFS is causing depression the reasons for this could be endless; if depression is causing CFS then we do not as yet seem to be able to cure CFS by treating with antidepressants.

### 2.2.2 Misattribution of physical illness as psychological/psychiatric illness

A recent article in the Psychologist (Goudsmit and Gadd 1991) points out a recent trend to consider cases as psychological/psychiatric when other conditions were the cause of the symptoms. They have two types of illustration: firstly cases like that of the famous cellist Jacqueline du Pre' who had MS but was told in the early stages that the symptoms were 'psychological' (Easton 1989). Secondly, and more seriously, studies that show the high level of undiagnosed serious illness (which would account for psychiatric disorder) in psychiatric hospital patients (Hall et al. 1981). Patients with myasthenia gravis are shown to suffer from delay in diagnosis due to misinterpretation of symptoms as psychological (Nicholson et al. 1986). Given the difficulty of diagnosing CFS and the ambiguity about the cause of its symptoms one should be careful in simply thinking of CFS as another form of depression, even though CFS patients show clear psychiatric problems.

### 2.2.3 Results on the MHQ

The CFS patients on the MHQ show to be more depressed, anxious, somatic, obsessional and phobic than controls. These results, particularly on the somatisation scale, support the view that CFS may be an illness where psychiatric problems are suppressed and appear as physical symptoms, as suggested by Wessely (1990(b)).

No differences are shown on the hysteria scale as one might expect from McEvedy's work that has labelled ME as hysteric. The failure of the Hysteria scale to show a difference may be to do with inherent problems with this scale, which suggests that it does not identify hysterical aspects so much as sociability (see Method 5.3.7).

Neurotic symptoms in CFS patients

CFS patients, according to the literature are more likely than controls to have high scores on neurotic-type psychiatric variables. Petersen et al. (1991) show CFS patients as high on hypochondrias, depression and hysteria (MMPI) and anxiety, neuroticism and emotionality. Stricklin et al.(1990) show Neuromyasthenia patients as high scoring on anxiety, stress and somatisation. Wessely and Powell (1989) show CFS patients as mainly depressed or somatising. CFS patients' MHQ responses suggest widespread psychological distress of a general nature. The MHQ questions centre on mild, rather than bizarre, psychological symptoms, e.g. "Do you worry unduly when relatives are late home?", "Can you get off to sleep alright at the moment?", "Do you feel panicky in crowds?" The literature and the evidence would suggest that CFS patients have a comprehensive set of neurotic type problems.

The evidence of general anxiety and depression, though not neccessarily at the clinical level, also suggests a neurotic tendency in CFS patients. CFS patients report feeling significantly more anxiety and depression than Crohns/colitis patients. CFS patients report less positively on the helpfulness of doctors. CFS patients had less expectation of getting well and more feel they are not coping with the illness. CFS patients,

therefore, are much more negative about their illness, despite the evidence that CFS does generally get better over time.

### 2.2.4 Symptoms, mood and depression

Correlations between symptoms, mood and coping are shown in Table 7. The analysis of the relationship between symptoms, mood and attitude is something which has not been fully explored and which highlights the inter-relatedness of the three.

Fatigue and symptoms correlate with depression score, anxiety and not being able to read well. The implication is that either depression (as indicated by the score) and anxiety increase perceived symptoms or that perceived symptoms increase depression and anxiety, unless the two are linked by severity of illness. However, results of the ANCOVA of depression and symptoms/fatigue show differences between CFS and controls are extremely significant even after depression is regressed out suggesting that depression is only one factor in the reporting of symptoms and fatigue.

### 2.2.5 Locus of Control

Locus of control work has not been thoroughly carried out on CFS patients up to recent years and may indicate something of the CFS patients' attitude to illness. The Health Locus of Control questionnaire shows us that CFS patients are more likely to attribute what happens to their health as due to chance. This means that CFS patients will not have a feeling of control over their illness, and this may both increase their proneness to chronic illness and impede recovery (see a review of this work by Reid 1984 p. 363). This type of attitude may also help assuage guilt according to Wessely (1990(b)) and be a sign that CFS patients could use their illness as a way to evade responsibility.

### 2.2.6 Depression and cognitive results

It is evident that CFS patients are depressed. CFS patients score highly on both the CES-D measures of depressed symptomatology and the more diagnostic MHQ measure of depression. It is evident that depression affects the speed tests, especially the psychomotor tasks. On the psychomotor tasks, however, we have improvement even after depression is taken account of in the regression. On the other speed tests the relationship is even more complex. Longitudinal testing shows that tests, like Digit Symbol test, which were performed poorly show recovery and an upward trend without significant change in depression. In Stroop the ANOVA at first testing suggests depression accounts for all the difference and improvement may be accounted for by the learning curve . However, in Digit Symbol depression as a covariate accounts for only part of the difference. One may conclude that although most of these psychomotor tests are linked to depression they may in fact be hiding an effect of CFS.

One might ask too if other negative psychological factors, as shown in the MHQ results, could have an effect on cognitive tests results. The use of anxiety in addition to depression in an ANCOVA does not significantly change the results. However there is little doubt that CFS patients do have high anxiety and depression scores and on the MHQ high obssessionality and somatisisation scores; therefore psychological, probably neurotic type, problems are indicated. These neurotic problems may affect cognition. It is not known, however, if CFS causes this or if it is causal in CFS.

The linking of perception that 'doctors are helpful' to 'less symptoms' and 'coping' suggest that doctors' helpfulness may make an important psychological, if not physical, contribution to improvement. Likewise the delay in diagnosis seems to have a negative effect on length of illness and symptoms, suggesting diagnosis may improve outcome both, in terms of length of illness and coping.

Not surprisingly, symptoms are linked to whether the subject is working and whether the subject is experiencing any problem with reading. What is not clear is whether this reading problem is an indirect measure of how able a person is to work or alternatively whether one can read directly affects a patient's choosing to go back to work.

## 2.3 Summary

The numbers of CFS patients with high previous serious illness, high numbers of antibiotics and high contact with CFS and related illnesses all suggest organic vulnerability to CFS, the causes being contagion and physical vulnerability.

However, the strong relationship with psychiatric variables suggests that CFS patients may be suffering, in part, from psychiatric symptoms. Whether these psychiatric problems are produced by or are a cause of the illness is another question. Locus of control questionnaire results also support the argument, since they indicate that CFS patients may be more external in their outlook on illness and/or that CFS patients' illness may be psychologically produced. CFS patients had more Life Events (causing stress) than controls. The evidence is that CFS patients tend to suffer from mild neurotic type psychological problems, and this may aggravate their illness and delay recovery. This study does support the view that demographic and prior health variables influence vulnerability and that depression and poor psychiatric profile are evident in those with the syndrome.

## 2.4 Recovery

### 2.4.1 Recovery of symptoms

The CFS patients show a reduction in symptom and fatigue measures at 2nd testing. These measures show that CFS patients' perception of their illness is changing during the period of illness. This is confirmed by the number of patients who considered that

they were getting better (67% of those who responded at first testing 60% at second testing). Since depression and anxiety are not substantially reduced in this period (more than controls), the diminishing of symptoms cannot be accounted for by improvement in mood. This reduction of symptoms is therefore most likely to be due to recovery, although an alternative explanation might be that patients are becoming habituated to some symptoms. The greatest change in symptoms is on "now" i.e. during the testing, rather than "this week" i.e. the week before, which suggests symptom reduction could be due to feeling more comfortable at second testing, although this is not shown in reduced anxiety levels. It is possible that this reduction in symptoms 'now' as opposed to symptoms 'this week' is because, when assessing symptoms at the time, the patient recognises the symptoms they have but on recalling symptoms they recall all the set of CFS symptoms, regardless of whether they had them that week.

It is important that the CFS patients appear to be recovering over the relatively short time, in relation to their illness, in which they are seen. The stated partial recovery of all but two CFS patients, combined with the reduction of patients symptoms, means that:-

1) CFS patients normally recover and, since no intervention was given (except the occasional patient trying folk remedies), this appears to be spontaneous.
2) Individuals within any group of CFS patients will be at a different stage of recovery when they are seen and there is no way of telling what stage an individual is at when he/she is tested. This means early, and more severely ill, patients are more likely to show abnormalities than patients who have recovered somewhat. The CFS patients show more variance and outliers in testing than controls which suggests that they have different severity and/or different rates of recovery from the illness.

### 2.4.2 Implication of recovery to the study

The conclusion is that CFS patients are not homogeneous. The cognitive problems observed in this study will depend on the severity of their illness and on the measure of recovery that has taken place. There are indications from the study that recovery,

though not necessarily complete recovery, (questionnaires given after the study was completed suggest eventual recovery to 90% capacity) is normal for CFS patients. The observations of the study, only two patients did not think they were better at second testing, and the literature suggest that recovery, though sometimes slow, occurs in the majority of cases and that deterioration is extremely rare. A small number of Royal Free cases had permanent muscle problems and recurrences of the symptoms in milder form and some patients appear to suffer from it for the rest of their lives (Royal Free disease: Channel 4, Akureyi: Hyde 1988, Wookey 1989). Deterioration does not seem to occur except in rare cases, normal progress is relapsing but improving, Clare (1991). Diana Longden (Longden 1989) is the one of the few cases, and the diagnosis is unsure, where deterioration has been recorded. If this study said nothing else the fact that it shows recovery of symptoms at the time of testing and improvement on some cognitive tests above that of controls is of paramount importance. This has not been sufficiently considered elsewhere; this may be because more intractable and severe cases have received more media attention.

## 2.5 Summary and model showing the implications of Section 2 for CFS

If aspects discussed above and the points of the literature survey are taken all together, a diagram of the factors involved in development of CFS could be displayed as that below (Figure 4).

There are five kinds of variables in Figure 4 which seem to increase vulnerability to CFS illness: these are demographic and geographic/occupational, as seen in the literature survey, and medical, psychological and psychiatric which are shown in the above results; all of these factors are higher in the CFS group but the illness itself seems to need some kind of trigger. Examples of these factors are:

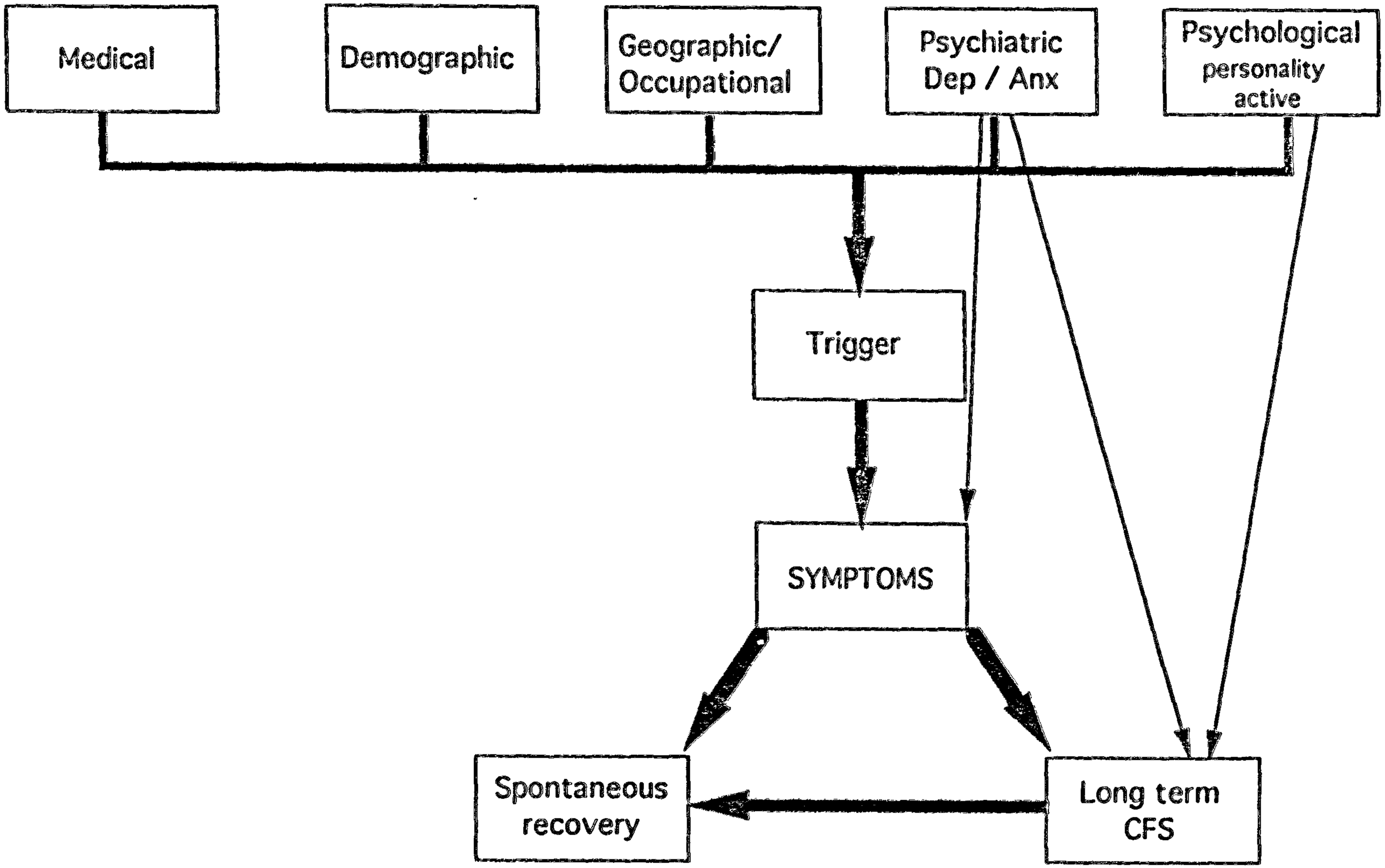



**Figure 4. Factors involved in the development of CFS**

- demographic: class, sex
- geographic: being in an area hit by trigger illness and/or CFS
- occupational: stressful job, teacher, nurse, doctor, in a large institution, working with others who get CFS
- medical: prior previous serious illness, contact with trigger illness
- psychological: personality, active
- psychiatric: previous psychiatric history, depression / anxiety
- trigger: stress (Life Event), viruses (EBV, Coxsackie B, Echo virus), medical operation.

These lead to increased likelihood of symptoms that become the CFS syndrome, but the symptoms seem to require a trigger, often viral, illness (related to geography or exposure via occupation) or possibly some stress factor. Depression and anxiety aggravate symptoms at all stages. Recovery takes place, but at differing rates which affects cognitive symptoms. Undoubtedly diagnosis and expectation of recovery will mitigate recovery; these are not shown on the diagram but it gives us some ideas as to the process of CFS.

## 3 The neuropsychology of CFS patients

### 3.1 Table of cognitive results, recovery and depression

This section discusses the results of the cognitive tests at:-

1) first testing comparing all three groups;
2) between CFS and normal groups at second testing and,
3) when depression score is used as a covariate, against results at first testing between CFS and normal controls.

A summary table (Table 16) follows; the last column indicates what possible causes may be implied from the results found.

**Table 16. Summary of results: page 1 of 2**

This Table summarises the test results. Results are shown for the three groups of subjects (CFS patients, normal controls and Crohns/colitis controls, abbreviated to CFS, N and C/C) on 19 measures taken from 14 cognitive tests. The first column shows the Type of Test, according to the key below. The differences at first test-session are shown in Columns 2-4 for each test, where "Y" indicates that a significant difference was found for that pair of groups according to a Scheffe test. The changes between first and second test-sessions are shown in Columns 5-9. In the first three of these columns, "Y" indicates that there was a significant Repetition effect (i.e. which test-occasion), Group effect (i.e. the subject group) and interaction between these two effects respectively when a mixed model Analysis Of Variance (ANOVA) with repeated measures was carried out; Column 8 shows whether the differential improvement in performance is likely to be due to a different starting-point on the learning-curve. Column 9 shows in general which group is improving differently from the other two groups, according to the graphs shown in Appendix 6 ("S" denotes all groups improving similarly). Columns 10-12 indicate whether depression has been shown to affect performance partly or wholly, as shown by ANCOVA analysis, where again "Y" indicates "Yes". The final column indicates whether Depression ("D"), CFS illness ("C") or Task demand, as discussed in Discussion Section 3.3, (T) or a combination is indicated as a possible cause of the differences found by the results.

Type of test: key

| | |
|---|---|
| A | Attention |
| c | Copying |
| C | Coding |
| D | Digit |
| L | Language |
| M | Memory |
| P | Psychomotor |
| sM | Sensory memory |
| S | Spatial |
| T | Timed |
| V | Visual. |

**Table 16. Summary of results: page 2 of 2**

| | | Differences | | | Improvements | | | | | Depression | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Type of test (code) | CFS worse than N | C/C worse than N | CFS worse than C/C | CFS and Normal Group repetition effect | group effect | interaction of both | Possible improve due to learning | C/C same improve (graph) | Not influenced | Part influenced | All depression | Difference due to (code) |
| Memory tasks | | | | | | | | | | | | | |
| (i) Language | | | | | | | | | | | | | |
| Logical memory | LM | Y | n | n | Y | n | n | Y | C/C | Y | | | A |
| Associate learning | LM | n | Y | n | Y | n | Y | ? | N | Y | | | - |
| Word recognition: | | | | | | | | | | | | | |
| (Correct) | LM | Y | n | n | Y | n | Y | ? | CFS | | Y | | DCA |
| (Correct-errors) | LM | Y | n | n | n | n | n | - | - | Y | | | CA |
| (ii) Other | | | | | | | | | | | | | |
| Digit forward+back | sM | n | n | n | Y | n | n | Y | C/C | Y | | | - |
| Rey memory | SM | Y | Y | n | Y | n | n | ? | C/C | | Y | | C? |
| Rey copy | Sc | n | n | n | n | n | n | - | - | Y | | | - |
| Visual span | SM | n | n | n | n | n | n | - | N | Y | | | - |
| Tasks requiring speed | | | | | | | | | | | | | |
| (i) Language | | | | | | | | | | | | | |
| Stroop: Reading | LT | Y | n | Y | n | Y | n | - | - | | | Y | D |
| Colours | LT | n | n | Y | n | n | Y | ? | - | | | Y | D |
| Word fluency: | | | | | | | | | | | | | |
| Hard letter | LT | n | n | n | n | n | n | - | C/C | | | Y | - |
| Categories | LT | Y | n | n | n | Y | n | - | C/C | | | Y | DA |
| (ii) Other | | | | | | | | | | | | | |
| Reaction time | | | | | | | | | | | | | |
| Decision time | P | Y | n | Y | Y | Y | n | Y | S | | Y | | DC |
| Movement time | P | Y | n | Y | Y | Y | Y | n | N | | Y | | DC |
| Finger Tapping | P | Y | n | Y | Y | Y | n | Y | C/C | | Y | | DC |
| WAIS Digit Symbol | PC | Y | n | Y | Y | Y | Y | ? | CFS | | Y | | DC |
| Threshold task | VA | Y | n | Y | n | n | n | - | N | Y | | | C? |
| PASAT | DA | n | n | n | Y | n | n | Y | - | | | Y | D |
| Visual spatial task | | | | | | | | | | | | | |
| WAIS blocks | S | n | n | n | Y | n | n | Y | C/C | Y | | | - |

## 3.2 Cognitive results at first Testing

At first testing CFS patients do worse on most of the tests. This is consistent with their complaints of cognitive difficulties. (At first and second testing CFS patients take approximately fifteen minutes longer to complete the same battery than normal controls; this suggests they are slower at tasks in general.)

### 3.2.1 Psychomotor Tests

The largest and most significant differences that occur, with both normal and chronic controls, are on tests which involve psychomotor speed or muscle co-ordination at speed. This could be due to a physical problem such as nerve impulse slowness and slowness of processing in the brain, but also, at least partly, to more psychological factors, since depressed patients are known to be slower on reaction times (Miller 1975). Evidence from the reaction time test suggests that CFS patients do not benefit from practise on these kind of tests but succumb to fatigue quickly and slow down during testing. In other words, psychomotor slowing may be increasing, when compared to controls, as the task progresses. The existence of such differences may relate to the lack of alertness and difficulties comprehending what was going on which the experimenter observed. The difficulties of CFS subjects in everyday life may not in fact be due to specific memory problems, but to problems of taking in information and responding to it at normal speed while a number of things are happening which call for their attention.

### 3.2.2 Memory differences

The memory differences found between CFS and normal patients are significant but small. The results of chronic (Crohns/colitis) patients' tests seem to show that they too might experience these difficulties to a lesser extent. This suggests that problems common to both CFS and Crohns/colitis groups may be impinging on memory function to a small degree or that normal controls might be performing better for some unknown

reason. The chronic patients did not complain about such memory problems, suggesting that CFS patients are particularly sensitive to these difficulties. Differences between CFS patients and normal controls on Associate Learning, Logical Memory and Rey Memory remain after taking depression score into account, which suggests these differences are not due to mood in chronic illness.

The Rey Memory differences are greatest between CFS and normals at first testing but group differences disappear when second testing is taken into account. This may be because at first testing subjects did not know they would be asked to remember the drawing and learning was therefore incidental. CFS patients, if they found copying harder, may have paid less attention to the pattern and learnt less incidentally than on second testing when they paid attention in order to remember. The fact that a few CFS patients fail to see the rectangle as a unit is related by Wilson and Binder (1982) to frontal and left hemisphere damage; it may be that poor strategy in this test may result in lower scores in these patients.

In the Associate Learning Task CFS patients have a tendency to mix up answers on Version Two, where a number of answers related to the same topic. They also seem less inclined (according to discussion with them) to use techniques such as imagery to link items.

CFS patients remembered the last five segments of the Logical Memory task less well than controls, but not the first five. It could be that CFS patients' learning abilities are defective in some way because they are remembering early material better than late material (Lezak 1983). However, the CFS patients performed well on immediate / short-term memory tasks, therefore this is more likely to be due to a drop in concentration.

The deficiency in word recognition is slightly worse than might be expected from other results and it may be that isolated words pose a particular recall problem. It is unlikely that CFS patients are malingering in their poorer results on these tests because they also

show significantly poorer scoring (at the 0.1 level) on the logical memory tasks and slightly worse on the Associate Learning task. The poor score for CFS patients at first testing for Word Recognition (correct) may be due to their strategy in not guessing names of which they are not sure. Depression affects the scoring on correct words only, not on correct minus incorrect. This suggests that guessing less words (whether correct or not) is related to being depressed.

From these comments, one can see that the problems may lie with strategies for coping with a task as much as with memory itself.

The memory differences of CFS and Crohns/colitis patients apply only to tests of memory involving recent/long term memory. Immediate/short term memory tasks, such as the Digit Span, show CFS patients doing as well as normals. This suggests that any memory differences that exist apply after the sensory memory stage. It may be that CFS patients have actual recent/long term memory problems, even if they are small, or as the differences are small the difference could be due to attention, arousal and task difficulty as discussed later.

The overall results of the memory tests suggest most patients are unlikely to have clinically significant memory differences that would cause noticeable problems for the CFS subject. However, because they occur concurrently with a much greater slowing down problem, the CFS patient is less likely to take in as much information and the problem maybe exacerbated.

CFS patients have notably more success with remembering of numbers and this may not be due to the difference between language and numbers but between recent/long term and immediate/short term memory. Another possibility is that CFS subjects have problems with retrieval where two close alternatives are available: on the word recognition test several pairs of words that were similar phonetically but not in meaning were presented in the recognition task. This would fit in with the word mistakes reported

in CFS such as blue and black, hot instead of cold.

The word category task is also significantly poorer (at the 0.1 level). This suggests that the word retrieval problem of CFS patients affects categorising by meaning more than by sound.

The Stroop task was particularly poorly done by CFS patients; this could be due to the need to process at speed and the need to inhibit an alternative response. Difficulty in reading fluency might be more of a factor, however, because the CFS patients score significantly worse ($p<0.01$) on the less difficult part of the Stroop test. The CFS patients do worse on reading the text in different coloured ink; the difference is more significant between the groups than on the more difficult and demanding part, Stroop colours. As the difference is on reading rather than colours, this suggests that many CFS patients have a problem with reading rather than interference in reading, although Stroop reading includes some interference. It is possible that both problems may occur. Further studies should perhaps test fast reading with no interference. This reading problem may relate directly to articulation slowing, due to motor slowing. Less likely, but possible, is a physical problem such as muscle weakness in the eye (Potazanick and Kozol 1992).

The CFS patients are poorer than controls on the Threshold task (between CFS and Normal controls the difference is $p<0.05$). This test involves vigilance, fast information processing and psychomotor skills. On this test the same differences are found between CFS and Crohns/colitis patients suggesting that this is a robust difference and peculiar to the CFS group. This also suggests a possible attention problem, however it is surprising that CFS patients do relatively well on the PASAT if they have an attention problem because it is quite a good test of divided attention.

## 3.3 Test performance and malingering, motivation, fatigue and attention

### 3.3.1 Malingering

If the test performance is due to psychological causes, depression is the main candidate.

Malingering is not suggested in Lezak's 15 symbol test or in performance of the Associate Learning task. Malingering in the context of these results seems unlikely, since it would be difficult and unlikely that malingering would produce such a pattern of slightly worse performance and differentiate between speed and memory tests.

### 3.3.2 Motivation and fatigue.

Lack of motivation seems a more possible explanation of poor test performance; but we are then faced with the problem of why Crohns/colitis patients should score with CFS on memory and with normals on speed. The pattern of poorer scores on speed tests compared to both groups does fit in with the CFS complaint of muscle fatiguability and fatigue. The normal controls came to us at the end of a winter working day; consequently many were fatigued. Clearly, CFS fatigue must be beyond this if it produces our effects. However, the CFS patients do worse on the Threshold task than controls which, according to Grafman et al. (1991), should show up a central fatigue problem. The Stroop test score has been found to be related to depression, it is also a test illiciting similar mistakes to those reported in CFS patients. Therefore the poor results in CFS patients may be caused for either of these reasons.

### 3.3.3 Test performance and the arousal curve

The CFS patients did superficially appear less alert at first testing and the much longer length of time (on average an estimated 1/4 to 1/2 an hour longer than controls at first testing) it took to test CFS patients might be due to problems of arousal. Subjects' general alertness and speed of response seem much poorer in the CFS group. It was often necessary to repeat instructions or deliberately recall the subject to what was being said. Speech in some CFS cases is also very slow. Alertness in CFS patients appears better at second testing in respect of following what was said and body language.

In the CFS patient, the lack of alertness observed at testing may be affecting test results; and this lack of alertness may be mitigated by the degree of arousal experienced in the person at the time. It is clear that on tests with a high psychomotor component and psychological tests CFS patients perform poorly at first testing, with some recovery at second testing. However, performance on the other types of tests leave a scattering of apparently unrelated significant scores. One possible explanation is to consider the task demand of each test in this group. Task demand was considered in terms of the level of task complexity and the length of time for which concentration is necessary. The task difficulty/attention allocation was then divided into low, moderate and high. In tests with extremely low task demand, i.e. Digit Span and Visual Span, CFS patients perform well. On tests with extremely high demand and high perceived difficulty, i.e. P.A.S.A.T. and Associate Learning (P.A.S.A.T. was perceived as the worst test), the CFS patients do well possibly because they are aroused and concentrate hard on the test. On tests with moderate task demand, the Logical Memory, Rey Memory and Word fluency categories, they do worse. In other words, test performance on non psychomotor tasks may be related to the arousal produced by tasks of different difficulty on a U shaped curve as shown in Figure 5. This U shaped curve is taken from putting tests into a low, moderate or high category of task difficulty and thus arousal elicited, and then arranging the test results in order of the percentage of the normal score gained by the CFS patients. The results show a good fit of score at first testing with a possible U-shaped arousal curve. In further support of this hypothesis is the poorer scoring of CFS patients on the last five sections of the Logical Memory test, which could be due to loss of attention/arousal by the end of listening to the test passage being read.

In contrast to CFS patients this pattern is not shown for Crohns/colitis patients at first testing; this is seen in Figure 6, where the Crohns/colitis results are shown with those of the CFS results, both sets of results having been treated in the same way (excluding PASAT, which was not carried out by the Crohns/colitis group in general), but do not produce any pattern.

Figure 5. U-shaped curve produced by taking percentage of CFS performance to Normal performance on non-psychomotor tests at first testing. The horizontal axis may represent the degree of arousal needed to perform the task.

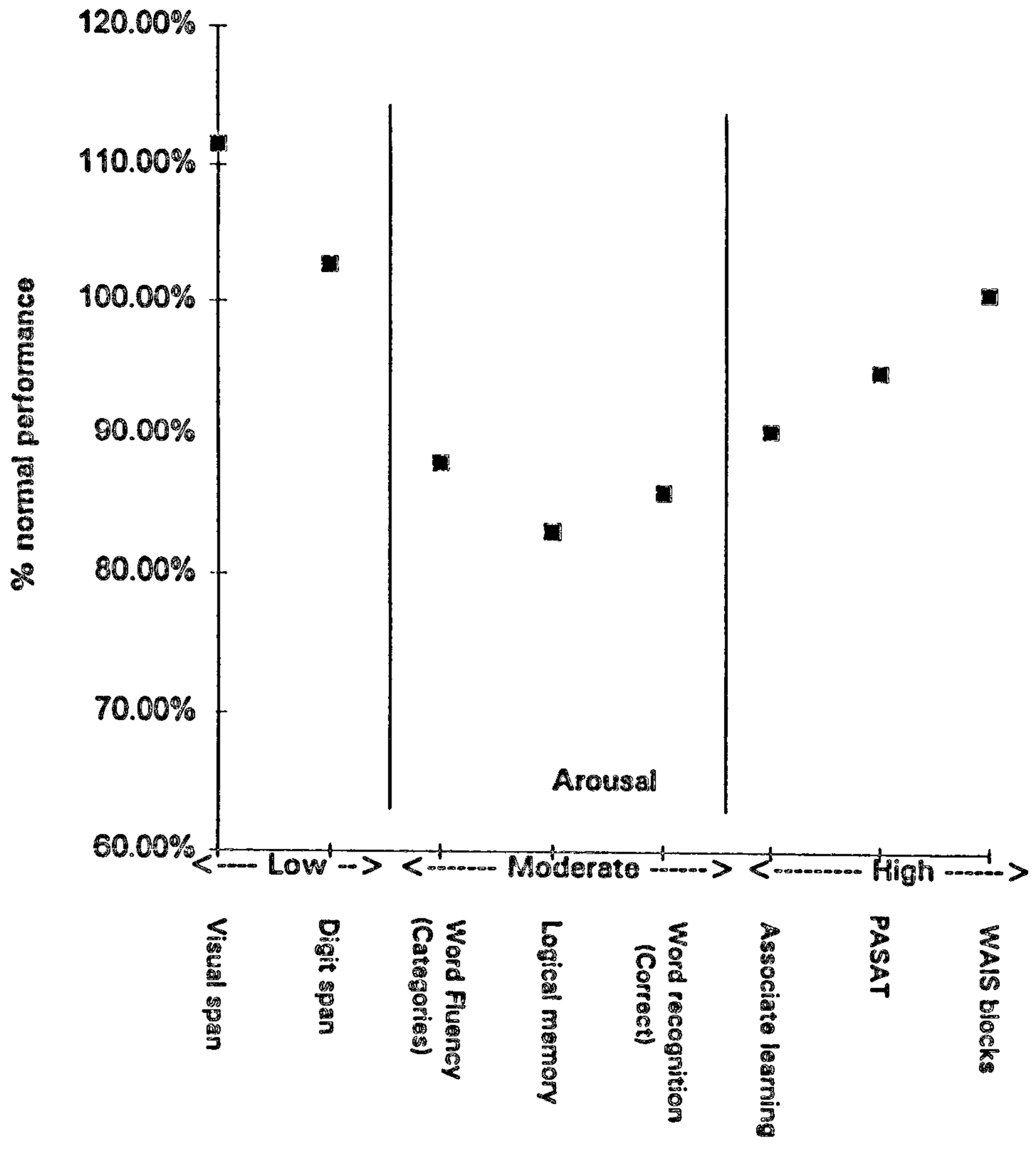
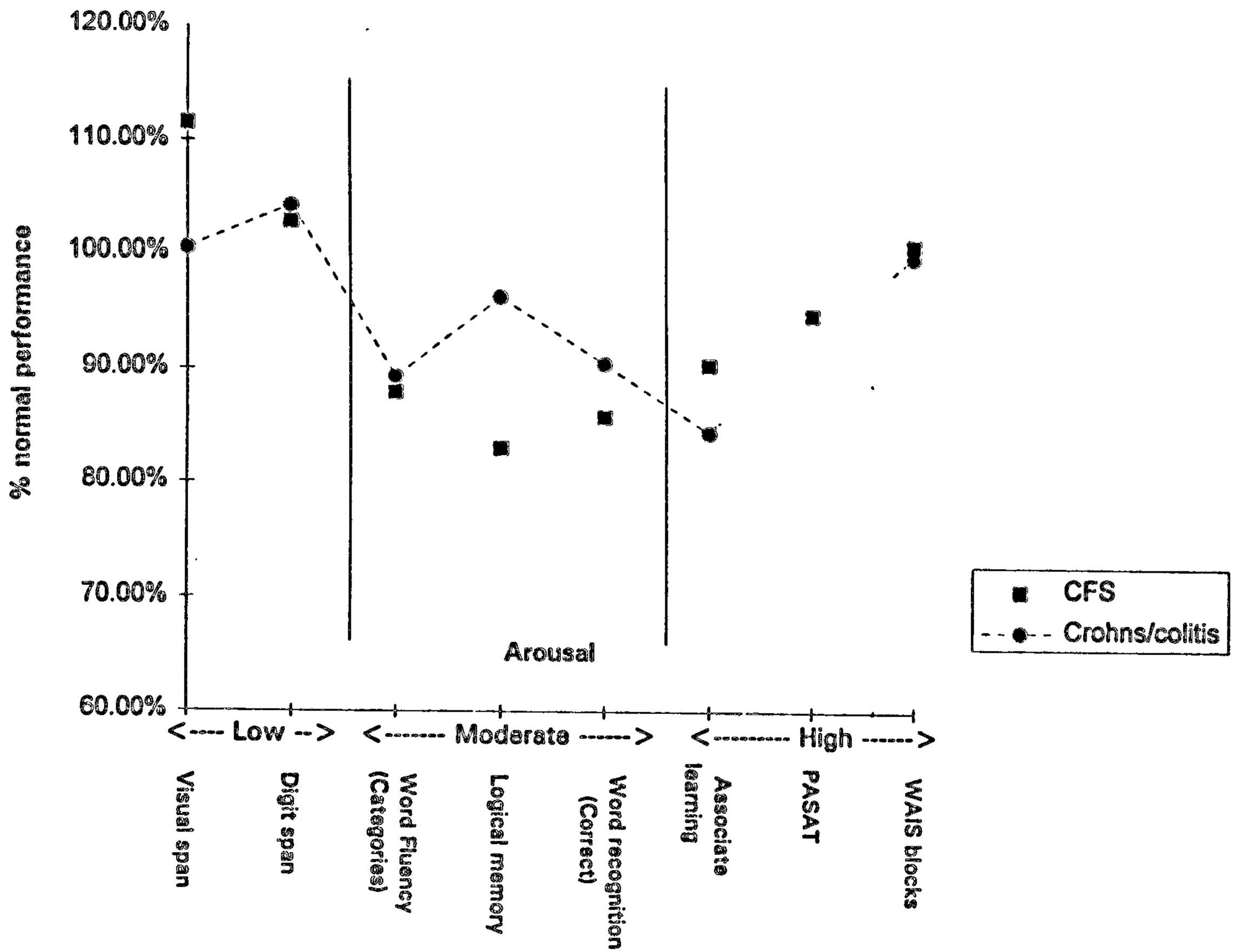


Figure 6. Comparison of CFS and Crohns/colitis curves produced by taking percentage of performance to Normal performance on non-psychomotor tests at first testing. The horizontal axis may represent the degree of arousal needed to perform the task.



### 3.4 Cognitive results at second testing

At second testing CFS subjects still show a significant difference to that of the normal control group in Stroop Reading, Reaction Time (both), Finger Tapping and WAIS Digit Symbol. These are mainly tests involving psychomotor skills or tasks under time restrictions and suggest that CFS patients have a continuing problem of psychomotor slowing and, possibly, speed of processing during their illness. These are tests where the Crohns/colitis patients generally score similarly to the normal patients, at first testing. Memory differences evident at first testing are now only seen as group differences on the Word recognition test and this suggests that the original memory differences are not of very great significance in showing an effect of CFS.

The study shows a pattern of cognitive problems consistent with most previous literature involving cognitive tests. These are that CFS patients are slower than controls in decision and movement time, on WAIS digit symbol and Stroop tasks and slightly poorer than normal controls on some verbal and visual memory tasks. The study observes improvement in CFS patients on a number of these poorly done tests during the recovery period. So it is possible that cognitive performance is depressed initially by the illness but recovers over time. Mood variables, although highly correlated to many of the cognitive tests, especially those involving speed, only partially account for test differences.

The study reported in this thesis shows that chronically ill patients are less good than controls on some memory tests, but function as well on psychomotor tests. It may be that being chronically ill, as for both sets of patients, affects performance on the tests, or that Crohns/colitis patients perform worse for different reasons, e.g. taking the drug sulphursalazine, or vitamin or electrolyte deficiencies. However, the Crohns/colitis patients tested do not show high scores on self rated depression symptamatology and anxiety, and this is unlikely to be the cause.

## 3.5 Recovery, improvement and the learning curve

Improvement at the second testing by CFS patients may occur because their poor performance at first testing makes improvement easy compared to control groups who may already be performing at ceiling.

The problem of retesting two groups when one group is already performing significantly worse at first testing is that the poorer group may improve spectacularly, due to practise or learning, when the group already scoring highly has already reached near to its ceiling. It is known that learning curves tend to be exponential, i.e. tailing off at the limits of the curve. In respect of the results of this study one needs, therefore, to consider whether, for each given test, practise or learning is known to produce the differential improvement seen.

There is in this study unlikely to be any effect from time delays between test and re-test. However the fact that CFS patients generally had longer between tests is likely to mean they benefitted least from practise and results are under stated. (For further discussion see "Method" Chapter.)

The following paragraphs discuss tests for which improvement is most seen.

Reaction Time: This is not a test that previous studies (Cronbach 1964) suggest is very responsive to learning or to practise, provided the same form of test is conducted and sufficient trials are used. The median score was used, not the mean, to allow for some slow responses at each testing. However, the normal group makes substantial improvement as well as the CFS group on decision time so this is probably due to practise or learning. Appendix 6 Graph 13 shows uniform slope of improvement in all three groups confirming that this is due to some practise effect. On movement this is not the case and small gains for the normal controls are matched by larger ones for the CFS and Crohns/colitis patients but this could still be due to learning if the learning curve for

this task flattened out very quickly. In the Finger Tapping task, CFS patients improved significantly compared to normals, but do not reach the score of the normal group. Therefore this could be due to learning. However, the Crohns/colitis group, also starting worse than the normals, show no improvement suggesting that the normals' improvement is just a minor fluctuation rather than the impact of learning.

In the Stroop reading test, CFS patients show improvements whereas the normal patients show no improvement, therefore improvement is probably not due to learning. If the CFS patients, over three performances on Stroop colours, are looked at (Appendix 6 Graph 10), however, the change for them looks as though it is part of a general improvement which brings them up to overtake the performance of the normal controls, suggesting improvement due to recovery not learning.

In the WAIS Digit Symbol test, large improvement in the CFS patients is matched with very small improvement in the normals but greater improvement (Appendix 6 Graph 16) in the Crohns/colitis group. Again this could be accounted for by a sharply flattening learning curve, or by recovery.

Rey Memory: The improvement on Rey Memory follow a similar slope for both CFS and normal groups, as shown on Appendix 6 Graph 6. Crohns/colitis patients improve much less despite the fact that Crohns/colitis patients started off worse than both CFS and normal groups.

Associate Learning: The use of two different versions of the Associate Learning test causes a negative learning effect at second testing, i.e. it appears that subjects do worse on the test, having previously been tested on the other version, than if they were doing the test for the first time. The results are rather confused, CFS and Crohns/colitis patients improving and normals declining in performance.

The differences in improvement between testings in CFS patients and controls probably show mostly in the reaction time movement time test, finger tapping and the WAIS digit symbol test. In order to remove the effects of differential learning, due to the groups position on the learning curve, subjects could have been asked to repeat the tasks until learning was extinct before measuring the results. In this study the increased length of testing that this would have involved would not have been practical.

Improvement in the Finger Tapping test is the least likely to have been affected by learning and most likley to show CFS improvement.

### 3.6 Useful tests in studying CFS.

Some tests seem to be very sensitive to CFS and to recovery, and therefore might be used to assess CFS patients; these are Reaction Time, Finger Tapping and Digit Symbol. The Stroop Test differences are highly correlated to depression symptomatology and therefore the results are less useful in the study of CFS. The Rey Memory test and Finger Tapping test are also possibly sensitive to CFS but do not recover in the time-span of this study. The Rey Memory Test seems the best memory test to use, especially if very severely affected people are being tested.

### 3.7 Test performance and neurological factors

In the absence of clearly defined neuropsychological deficits in CFS, one can only speculate which areas of the brain, if any, might be suspected to be a factor. However, the results, perhaps, offer the following possible avenues for further study.

1. CFS patients seem to have a problem with speed of movement and response which is probably due to a central fatigue or psychomotor problem.
2. CFS patients show evidence of psychiatric problems, especially depression and anxiety. These may be pre-existent to the illness and probably causal. However if they are not pre-existent they suggest that CFS creates depressive illness.

The results suggest the following possible problems:

3. There may be a slight memory/ recall problem in CFS related to an illness factor shared with chronic patients.
4. CFS patients may have problems with visual search tasks and visual memory tasks.

The literature shows that other problems - sleep irregularities, inappropriate physiological arousal and abnormal rest /work cycle - are indicative of other areas such as the hypothalamus or hippocampus. It is unlikely that CFS patients are suffering permanent damage because the results discussed do not indicate anything of this kind and recovery is almost universal in CFS subjects. However, current work (Hyde, Goldstein and Levine, 1992; Hyde, Biddle and McNamara, 1992) suggests that there may be blood flow abnormalities in the brain or disruption of hormonal and endocrine secretions. The high incidence of depression is suggestive of a neuro-transmitter imbalance. We should not overlook the possibility of a pathology in the brain of a subtle nature. In particular, residual problems in patients with good psychological recovery should be studied.

The areas of the brain which the literature suggests are involved in CFS and which are in accord with the conclusions of this study are the hypothalamus and the temporal lobe. The hypothalamus is suggested because of the factors mentioned above. It is also next to the pituitary gland and there is evidence that the pituitary gland is affected. Temporal lobe damage, or poor blood supply to the temporal lobe, could account for a number of factors present. It could account for poor Rey Complex Figure memory results. Verbal and visual anomalies in recall would depend on the side most affected. Poor categorising and deficits in visual illusion might also occur if the temporal lobe was affected. The temporal lobe also has an effect on mood, and personality changes are seen in temporal lobe epilepsy. WAIS Digit Symbol, Lezak (1983 p.273) reports, is a good test of minimal brain damage, but tends to be affected regardless of location.

One area therefore that could be indicated as being involved in CFS is the limbic system. The following points give supporting reasons for limbic system misfunction in CFS.

However, the results discussed in relation to memory are not sufficient to indicate pathology in this area.

1) Analysis of the brain's blood flow in some CFS patients suggests that this area is affected. (Mena and Villanueva-Meyer 1992).
2) Damage in this area could account for visual spatial impairment and verbal memory impairment depending on the side involved.
3) The hypothalamus could be involved in problems with regulatory systems (heat, time clocks etc), which might account for sleep abnormalities and arousal being inappropriate to time of day.
4) Damage to the limbic system could account for emotional changes, depression anxiety, agitation and impulsivity in CFS patients.
5) Damage to the limbic system has been discovered in severe inflammatory and viral diseases (Heilman et al. 1985 p.391) which relates to CFS etiology.

No clear signs of brain damage or cognitive deficit are found in the results. The results show psychomotor slowing that need not be due to brain damage.

Psychomotor problems

It is quite clear from these results that the CFS patient has a motor slowing problem. As for motor problems, in CFS the general slowing problem might be to do with slowing of nerve impulses or synapses relaying the message to the muscle. It could be to do with damage to the muscle itself, or problems in the cerebellum or cortex. However it is more likely to be a generalised problem, and the sluggishness of response could relate to blood flow abnormalities in the brain.

Minor Head Injury (MHI) and neurology of CFS

This study has mentioned similarities with MHI patients. The symptoms of patients with minor head injury are very similar to those reported by the CFS patients. Studies (McLean 1983; MacFlynn et al. 1984) of MHI patients on neuropsychological assessment show they initially have problems with the Stroop and four choice reaction time but that

these recover within one month to six months. Dikmen et al. (1986(b)) found, at 3 days after MHI, differences between patients and controls on immediate and delayed recall, delayed recognition, seashore rhythm test and sum recall and the Stroop. However, after one month only seashore rhythm test and a four hour recall test showed any differences.

Amongst the possible causes of MHI after-effects that have been suggested are reduced cerebral blood flow, altered brainstem evoked potentials and reduced speed of information processing, all of which are also indicated in CFS.

It can be concluded that MHI patients experience similar neuropsychological problems to CFS patients, possibly due to similar neurological problems but comparison of this study and Dikmen's (Dikmen et al. 1986(a), 1986(b)) suggest MHI patients have less severe problems and recover faster than CFS patients.

The wide spread of neurological symptoms in CFS suggests that, if the brain is involved, more than one area is indicated, i.e. a diffuse rather than focal problem. There is indeed no clear evidence from this study that the problems found in CFS patients involve any neurological abnormality other than that found in depressed patients.

**4. Comparison with previous neuropsychological testing**

Altay (1990) finds that CFS subjects are all significantly better than normal controls on a similar test battery. The results of the study reported in this thesis conflict with this particularly on Digit Symbol. However, Altay's controls are only matched on age and, since CFS patients are typically of high IQ and educational level, this could account for the differences between Altay's CFS patients and controls. Indeed, as discussed previously, the study reported here does not suggest CFS patient differences with controls are necessarily below average (although they would be on reaction time and other psychomotor tasks) but simply below performance for matched groups.

Prasher, Smith and Findlay (1990) from evoked potential examination in CFS patients suggest two subgroups of CFS patients, one with attentional deficits and the other with slower speed of information processing. The study reported here fits in with both of these findings.

Kilfedder (1988) and Smith (1991) both show slower reaction time in CFS patients. The study reported here confirms that result and shows that it is likely that this effect is due partly to depression. The study also shows that improvement occurs in movement time.

Wechsler's memory scale is used in Kilfedder's and Bastien's research. In the larger study Bastien (1992) finds significant deficit in verbal and visual recall on the scale. This study also finds poorer performance on verbal recall on Weschler and Visual recall problems on the Rey Complex Figure. However, these differences in the study reported here are not sufficient to qualify as deficits i.e. outside normal range.

Smith (1991) shows Stroop effects on the equivalent of our reading test. The study reported here confirms this, but the results suggest this is not due to distraction. The study reported here also shows that CFS patients' performance seems to be affected by depression, so much so that depression might account for this difference.

Bastien shows drawing to be poor in CFS patients. The study reported here does not find this; Rey Copy is not significantly worse in the CFS group, although this effect may occur only with drawing not with copying. It is, however, likely that differences might have occurred if CFS patients had been timed on the copying task. The Complex Figure test is much worse from memory, more at first than second testing (where the need to remember was known), and this may reflect drawing problems.

Smith finds CFS patients slower and less accurate in visual search tasks; this study does suggest that CFS performance is poorer on the Threshold task which is similar in its visual search requirements.

Lane (1991) finds a discrepancy between visual and verbal memory. This study finds CFS patients poorer on both. However the fact that no significant difference is found on Visual Span suggests visual drawing (as above) may be a factor.

**Summary**

In comparison with past studies the study reported here confirms that CFS patients probably have reaction time slowing (DT and MT); movement time improves with recovery in our study. CFS patients have a problem with the Stroop task but this may be due to depression. CFS patients may have minor verbal memory (not immediate/short term memory) problems but not large deficits on these tasks, except possibly in very ill groups. CFS patients probably have problems on visual search tasks and the Rey Memory task. In addition the study shows the CFS patients to be much worse on the WAIS Digit Symbol and this appears only partly accountable by depression. This study indicates the severest problems for CFS patients may be in psychomotor slowing.

# 5 Summary of Discussion

## 5.1 Results

The results show:

1. CFS patients perform below controls on psychomotor tasks and recent/long term, but not immediate/short term, memory tasks
2. CFS patients improve on second testing, above improvement in normal controls, on some of the tasks where they performed worse than controls at the beginning but some of this could be due to differential learning.
3. CFS patients score highly on self-rated depressive symptomatology and anxiety, which partially accounts for their poor performance on cognitive tests.

## 5.2 Implications

1. CFS may cause a decline in neuropsychological performance.
2. Psychomotor slowing is a problem for CFS patients.
3. Depression is an important factor in CFS.
4. Spontaneous recovery occurs in neuropsychological problems in CFS patients over the course of a year but may be negligible in the improvement of mood.

Previous research has proved the existence of high depression sores in CFS patients. This study shows that mood scores do have a relationship to memory and psychomotor scores in CFS patients, although they do not necessarily account for the extent of psychomotor retardation and poorer cognitive performance. This relationship is not demonstrated in other studies although it can be assumed.

## 5.3 Contribution of results to knowledge of CFS

The study shows that CFS patients do less well on memory and psychomotor tests than matched normal and Crohns/colitis controls and this can be seen in small groups of moderately ill CFS patients. The CFS patients do consistently and markedly worse on psychomotor tasks and, although results seem to be affected by depression, analysis suggests depression does not wholly account for these differences. The CFS patients do worse on visual search tasks but only at first testing. The CFS patients also do worse on the Stroop and word fluency (language tasks) but these can be accounted for by depression. The study is not a replication although other studies discussed in the literature survey do show some of these results. The importance of this study is that it is a controlled study using a formal test battery (based on similarities to diffuse head injury and toxic poisoning) and looking at longitudinal changes in the results.

This study is unique in showing how CFS patients improve on some cognitive tests during recovery. It demonstrates that recovery may be occurring and that cognition and

psychomotor performance may be related to recovery. This recovery in cognition is concurrent with recovery in depression and anxiety, but recovery later is so small (in relation to the overall score) that it suggests that psychological variables are not the only factors in recovery. This study increases our knowledge about factors associated with vulnerability to CFS. The study increases our understanding of the memory and psychomotor problems of CFS patients and the study demonstrates how recovery may be occurring in these processes.

It is probably the combination of memory and speed of response rather than the specific problems that cause CFS patients to complain of problems with cognition. The largest, and probably the most disabling to the patient in the everyday, are the slowness and, possibly, a lack of alertness; this makes some improvement over time. It is tempting to see the treatment of depression as the answer to such problems but so far this has not been established. Rather, depression seems an integral part of the illness. If counselling and/or drugs can be shown to speed this recovery or the lifting of depression, this would be valuable and might improve psychomotor speed.

The CFS patients do worse on tasks that required mainly psychomotor skills. The results suggest psychomotor impairment which is aggravated by depression. The existence of specific focal impairment is not supported by the study and the best comparisons would be with diffuse head injury and conditions with general psychomotor retardation. The evidence recently brought forward as to decreased blood flow to large areas of the brain is supportive of generalised brain dysfunction (Mena and Villneuva-Meyer 1992).

# CHAPTER 6. CONCLUSIONS

The literature showed that a longitudinal study of testing CFS patients on a neuropsychological test battery would fill a gap in the literature and provide evidence as to the role of cognitive problems in CFS. The study described in this thesis used defined criteria for selection of patients, two control groups (normals and Crohns/colitis), and controlled for IQ in order to avoid the methodological problems of earlier research. It also excluded groups unsuitable for neuropsychological testing. The existence of high levels of depression was taken into account in evaluating the results.

The results show the following (statistical significances given are for the CFS group compared to the normal control group):

- CFS patients perform significantly worse than normal controls on 9 out of the 14 cognitive tests used in the neuropsychological test battery and significantly worse on all measures of psychiatric indicators, symptoms and fatigue.
- CFS subjects are significantly slower on psychomotor tasks than both normal controls and Crohns/colitis patients. These tests included Reaction Time (Movement Time $p<0.001$ and Decision Time $p<0.001$), Finger Tapping ($p<0.001$), and WAIS Digit Symbol ($p<0.001$).
- CFS patients are also poorer than both control groups on the Stroop Test reading ($p<0.01$) and Threshold Task ($p<0.05$).
- When self-rated depression symptoms score is used as a covariate it is found that depression could account for the differences on Stroop and part of the differences on the other psychomotor tests. However, highly significant differences remain on the psychomotor tests after depression is taken into account.
- CFS patients are also, but less significantly, worse than normal controls on memory tests: Wechsler Logical Memory Task ($p<0.1$), Word Recognition ($p<0.05$) and Rey Memory ($p<0.01$). These are tests of recent/long term memory; they show no differences on immediate/short term memory tests. Tests of recent/long term memory are, however, performed worse by Crohns/colitis patients compared to normal controls

on Associate Learning and Rey Memory. This suggests that both CFS and Crohns/colitis groups may have slight memory problems, but the scores for all groups was so high that performance for all groups was above average.

- CFS patients continue to perform worse than normal controls at second testing on Stroop Reading, Reaction Time, Finger Tapping and Digit Symbol (i.e. the difference in improvement is not significant). However, they improve more than normal controls do (i.e. the difference between the groups becomes smaller) at second testing on Associate Learning, Stroop Colours and WAIS Digit Symbol (each at $p<0.05$) and Word Recognition and Reaction Time (Movement) (both only at $p<0.1$). This improvement may be due to differential rates of learning on the learning curve or to recovery.
- CFS patients do not show improvement (beyond that of controls) on depression symptom scores and anxiety or fatigue but they do show small improvement above the normal group on symptoms that week ($p<0.1$).
- CFS patients' performance on psychomotor tasks shows that CFS patients have a problem with slowing of decisions and movement. These tasks show improvement when retested after a period of more than 4 months. These differences are partially accounted for by depression. CFS patients probably have a psychomotor slowing problem due to a combination of depression and CFS, which responds to recovery.
- CFS patients show very high levels of self-reported depression symptoms and anxiety throughout their illness despite the exclusion from this study of subjects with a psychiatric history or who are taking antidepressants. CFS patients also score highly on neurotic psychiatric indicators on the MHQ questionnaire. It is clear that psychiatric factors are important in CFS but that they are not necessarily there pre-illness nor do they wholly account for differences in cognitive performance.
- The results show that CFS patients have significantly different pre-illness experience (or perception of it). They have had more serious illness and more antibiotics.
- Once ill CFS patients have more problems with everyday activities and do fewer housework tasks and social activities than Crohns/colitis patients.

CFS patients are distinctive in their pre-illness experience and greatly reduce their activity even after the acute phase of their illness. The study does not find clear evidence of cognitive deficit, apart from psychomotor slowing, or evidence which would be highly indicative of the presence of brain damage. It does confirm the presence of high levels of depression and anxiety in CFS patients and it does find evidence of psychomotor slowing in CFS patients. Tests most sensitive to CFS seem to be psychomotor tests i.e. Reaction Time, Finger Tapping and WAIS Digit Symbol.

On non-psychomotor tasks, CFS patients are significantly, but only slightly, different when compared to normals on some memory and language tests and very little different from Crohns/colitis patients who also score significantly differently from normal controls on some of these tests. It might be suggested that one reason for the difference, between CFS and normal controls on these tasks, is that CFS patients may do worse on tests of moderate task demand than they do on tests of low or high demand, and this may be due to state of alertness / arousal.

No evidence is found in this study that CFS patients deteriorate on cognitive tests after initial testing; indeed there is an apparent trend for them to improve on some tests where they have poorer scores than controls at initial testing.

CFS patients have consistent and highly significant psychomotor slowing on the relevant tests, compared to both groups of controls. This slowing can only partly be accounted for by depression and is, therefore, probably due to some extent to CFS. It could be due to muscle and transmission problems or to neurological problems.

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# APPENDIX 1

# TABLES FOR LITERATURE SURVEY

## Appendix 1 Table 1. Definitions of CFS

### A. Holmes et al. 1988/1991 Centre for Diseases Control

### Definition of CFS

Major criteria
(1) Persistent or relapsing fatigue or easy fatiguability that
    (a) does not resolve with bed rest
    (b) is severe enough to reduce average daily activity by > 50%
(2) Other chronic clinical conditions have been satisfactorily excluded, including pre-existing psychiatric diseases

Minor criteria
Symptomatic or historical criteria: persistent or recurring symptoms lasting > 6 months:
(1) Mild fever ( 37.5 C - 38.6 C oral if documented by the patient) or chills
(2) Sore throat
(3) Lymph node pain in anterior or posterior cervical or axillary chains
(4) Unexplained generalised muscle weakness
(5) Muscle discomfort, myalgia
(6) Prolonged ( >24 h ) generalised fatigue following previously tolerable levels of exercise
(7) New generalized headaches
(8) Migratory noninflammatory arthralgia
(9) Neuropsychological symptoms
    (a) photophobia
    (b) transient visual scotomata
    (c) forgetfulness
    (d) excessive irritability
    (e) confusion
    (f) difficulty thinking
    (g) inability to concentrate
    (h) depression
(10) Sleep disturbance
(11) Patients description of initial onset of symptoms as acute or sub-acute.

Physical criteria : documented by a physician on at least two occasions at least 1 month apart:
(1) Low-grade fever
(2) Nonexucdative pharyngitis
(3) Palpable or tender anterior or posterior cervical or axillary lymph nodes (<2cm in diameter)

CDC exclusions Holmes et al. 1988 (summary Benatar 1988)
Diseases to be excluded before diagnosing CFS

1. Infections
Localised, occult abscesses
Chronic or subacute bacterial diseases, e.g. brucellosis (in 1988 criteria Lymes disease example not brucellosis), infective endocarditis or tuberculosis
Spirochaetal infection (e.g. Lyme disease)
Fungal infections (e.g. histoplasmosis, blastomycosis or coccidiodomcosis)
Viral infection (e.g. HIV infection)

2. Parasitic disease (e.g. toxoplasmosis, amoebiasis, giardiasis or helminthic infestation)

3. Malignant disease

4. Auto-immune disease

5. Chronic psychiatric illness (including endogenous depression, hysterical personality, anxiety neurosis and schizophrenia). *This exclusion was changed in 1991 to prior psychiatric history.*

6. Chronic use, abuse or side effects of prescription or illicit drugs (e.g. major tranquilisers, lithium, antidepressants, alcohol, heroin and marijuana)

7. Toxic agents (e.g.chemical solvents, pesticides and heavy metals)

8. Chronic 'inflammatory diseases (e.g. sarcoidosis Wegener's granulomatosis and chronic hepatitis)

9. Neuromuscular disease (e.g. myasthenia gravis or multiple sclerosis)

10. Endocrine diseases (e.g. hypothyroidism, Addison's disease, Cushing's syndrome and diabetes)

11. Chronic disorders (e.g. pulmonary, cardiac, gastrointestinal, hepatic, renal, and haematological diseases)

Appendix 1 Table 1 continued

B. Lloyd et al. 1988 (taken from Hickie et al. 1990)
Definition of CFS
(Note that Lloyd took part in Holmes et al.'s definition above).

To fulfil the criteria a patient must have chronic, persistent or relapsing fatigue of a generalised nature, causing major disruption of daily activities, present for more than six months, plus two major and three minor criteria (symptoms, signs or assessments):

(a) Symptoms: persisting at least six months continuously, or relapsing on three or more occasions with a similar pattern over six months or more.
(i) Major: concentration/memory impairment
(ii) Minor: myalgia, arthralgia, depression, depression, tinnitus, paraesthesia, headaches.
(b) Signs: Present on at least one occasion subsequent to the initial illness:
(i) Major: lymphadenopathy
(ii) Minor: pharyngitis, muscle tenderness.
(c) Immunological assessment
(i) Major:cutaneous anergy, T4 or T8 lymphopenia
(ii) Minor:hypoergy

Assessment of patients included tests for thyroid, neurological, haematological, hepatic, renal, or autoimmune dysfunction.

C. Dawson 1990 (quoted in Lynch, Seth, Montgomery 1991)
Definition of CFS

Syndrome with fatigue as principal symptom
Definite onset (not life long)
Fatigue is severely disabling and affects physical and mental functioning
Other symptoms may be present, particular myalgia, mood disturbances, sleep disturbance
Minimum six months of fatigue present at least 50% of time

Suggested baseline investigations
After comprehensive physical examination, including central and peripheral nervous system:
Haematology: haemoglobin and other parameters, differential B12 and folate, monospot
Biochemistry : profile of serum urea and electrolytes, glucose, liver and thyroid function, muscle (including cardiac) enzymes
Virology/bacteriology: at present this is controversial, but the most widely reported screening tests are for monospot and the VP-1 antigen if available.

Psychiatric assessment
Psychiatric diagnosis ought to be considered:
If depressive or anxiety symptoms are prominent and could predate the onset of symptoms

Appendix 1 Table 1 continued

If there is a strong family psychiatric history or past psychiatric history OR
If the somatic complaints are bizarre or inconsistent.

D. Ho Yen (1990)
Microbiology Dept, Raigmore Hospital, Inverness
Definition of PVFS/ME

1. Generalised, relapsing, fatigue exacerbated by very minor exercise causing disruption of usual daily activities for at least 3 months.

2. A complaint of prominent disturbance of concentration and short term memory impairment.

3. Exclusion of other organic causes for a similar syndrome.

Supportive evidence:
a) History
i) patient well before illness
ii) an initiating viral infection
iii) myalgia
iv) arthralgia
v) headaches
vi) depression
vii) tinnitus
viii) paraesthesia
ix) sleep disturbance (usually more sleep needed)
x) adverse effect of alcohol
xi) adverse effect of heat

b) Clinically
i) lymphadenopathy
ii) localised muscle tenderness
iii) pharyngitis

c) Laboratory
i) evidence of viral infection
ii) abnormalities of T cells

Appendix 1 Table 1 continued

E. Sharpe et al. (1991)

*Syndromes*
Two broad syndromes can be defined:

*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) The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50%of the time.
(e) Other symptoms may be present, particularly myalgia, mood and sleep disturbance.
(f) Certain patients should be excluded from the definition. They include:
(i) Patients with established medical conditions known to produce chronic fatigue (e.g. severe anaemia). Such patients should be excluded whether the medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination performed by a competent physician.
(ii) Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion.

*Post-infectious fatigue syndrome (PIFS)*
This is a subtype of CFS which either follows and infection or is associated with a current infection (although whether such associated infection is of aetiological significance is a topic for research). To meet research criteria for PIFS patients must
(i) fulfil criteria for CFS as defined above, and
(ii) should also fulfil the following additional criteria:
(a) There is a definite evidence of infection at onset or presentation (a patient's self-report is unlikely to be sufficiently reliable).
(b) The syndrome is present for a minimum of 6 months after onset of infection.
(c) The infection has been corroborated by laboratory evidence.

F. McKenzie Criteria 1988 from Blakely et al. (1991) (New Zealand study)

An illness duration of more than 6 months; a history of relapse; chronic fatigue; muscle pain; and early signs of muscle weakness on exercise.

G. Whelton, Salit and Moldofsky (1992)

CFS was defined as the occurrence of new complaints of exhaustion and weakness persistent or recurrent for more than 6 months after a "flu-like" illness. Patients were excluded if similar symptoms were present before the infection, or if there was any underlying primary medical or psychiatric illness.

# Appendix 1 Table 2. Names for CFS

*The following descriptive names have been compiled from the work of Dr. Gordon Parish, Dr. David S. Bell, Dr. Henri Rubinstein and Dr. Byron Hyde. The following represent just a few of the names that have been given to this protean illness:*

**The Poliomyelitis Names:**

A disease resembling or simulating poliomyelitis; atypical poliomyelitis; abortive poliomyelitis, encephalitis simulating poliomyelitis; encephalitis resembling poliomyelitis; postpolio syndrome; posterior poliomyelitis, sensory poliomyelitis.

**Names based upon location:**
Iceland disease, Akureyri disease, Coventry disease, Tapanui flu, Otago mystery disease. Royal Free disease, Lake Tahoe mystery disease, Lyndonville chronic mononucleosis, the English disease;

**Neuromyasthenia-names:**
Neuromyasthenia, Neurasthenia, Epidemic neuromyasthenia, Epidemic pseudo myasthenia, Sporadic postinfectious neuromyasthenia, Neurocirculatory asthenia;

**Myalgic Encephalomyelitis names:**
Myalgic encephalomyelitis, benign encephalomyelitis, benign myalgic encephalomyelitis, benign subacute encephalomyelitis, epidemic myalgic encephalomyelitis or encephalomyelopathy, acute infective encephalomyelitis, epidemic diencephalomyelitis, lymphoreticular encephalomyelopathy;

**Myalgia type names:**
Epidemic malaise, persistent myalgia following sore throat. Damadian's ache, Myofascial syndrome, Muscular rheumatism, Fibromyalgia syndrome, Fibromyositis, Fibrositis, Epidemic myositis, Lymphocytic meningo encephalitis with myalgia and rash, Syndrome polyalgique idiopathique diffus (S.P.I.D.);
*(The Fibromyalgia names are based upon a symptom complex seen in M.E., Lupus, Rheumatoid arthritis and several other non-associated illnesses.)*

**Personal names:**
Da Costa's Syndrome, Beard's disease;

**Symptom based names:**
Chronic fatigue syndrome, CFS, La Spasmophilie, (France), Raggedy Ann Syndrome, the English sweats, Effort syndrome, Tétanie chronique idiopathique;

**Bacterial names:**
Chronic brucellosis, Chronic lyme disease;

**Combined virus/symptom names:**
Post-viral fatigue syndrome, PVFS, Persistent viral fatigue syndrome;

**Immune based names:**
Chronic immune activation syndrome, CIAS, Chronic immune dysfunction syndrome, CIDS, Low natural killer cell syndrome (Japan), Multiple chemical sensitivity syndrome, Ecological disease, Allergic fatigue syndrome, Antibody negative lupus, Antibody negative lyme disease, Chronic activated immune dysfunction syndrome, CAIDS, Chronic fatigue and immune dysfunction syndrome, CFIDS, Naxalone-reversible monocyte dysfunction syndrome (NRMDS);

**Epstein-Barr Virus based names:**
Chronic Epstein-Barr virus syndrome, CEBV, Chronic active Epstein-Barr virus infection, CAEBV, Virus epidemic in recurrent waves, Chronic mononucleosis, Familial chronic mononucleosis, Chronic infectious mononucleosis, Chronic active Epstein-Barr virus infection, Chronic mononucleosis-like syndrome;

**Hypothalamic Names:**
Epidemic vegetative neuritis, Neurocirculatory asthenia, vasoregulatory asthenia, vasomotor instability, vasomotor neurosis. Habitual chronic hyperventilation syndrome;

**The Atypical Names:**
Atypical multiple sclerosis, Atypical migraine;

**Media names:**
Yuppie flu, Yuppie plague;

**Miscellaneous names:**
Soldier's heart, Epidemic vasculitis syndrome.

Taken from Hyde 1992a.

## Appendix 1 Table 3. Outbreaks of ME (CFS)

| Year | Place | Number of cases | Nature of epidemic |
|---|---|---|---|
| 1950 | Louisville, Kentucky, USA | 37 | Student nurses |
| 1952-54 | Denmark | over 70 | District |
| 1952 | Lakeland, Florida, USA | over 27 | District |
| 1952 | Middlesex Hospital, London | 14 | Student nurses |
| 1953 | Coventry, England | over 13 | Hospital staff |
| 1953 | Rockville, Maryland, USA | 50 | Student nurses |
| 1954 | Tallahassee, Florida, USA | 450 | District |
| 1954 | Seward, Alaska | 175 | District |
| 1954-55 | Johannesburg, South Africa | 14 | District |
| 1955 | Durban, South Africa | 140 | Hospital staff |
| 1955 | Berlin, Germany | 7 | Military |
| 1955 | Boscombe, England | 2 | Hospital staff |
| 1955 | Dalston, England | 233 | District |
| 1955 | Royal Free Hospital, England | 292 | Hospital staff |
| 1955 | Perth, Australia | Not recorded | District |
| 1955 | Gilfach Goch, South Wales | Not recorded | District |
| 1955 | Segbwema, Sierra Leone | 45 | District |
| 1955 | Thorshofn, Iceland | 114 | District |
| 1955-56 | North West London | 34 | District and Hospital staff |
| 1955-56 | Ridgefield, Connecticut, USA | 70 | District |
| 1956 | Coventry, England | 7 | District |
| 1956 | Pittsfield, Massachusetts, USA | 7 | District |
| 1956 | Punta Gorda, Florida, USA | over 150 | District |
| 1956 | Newton-le-Willows, Lancashire, England | over 162 | District |
| 1957 | Brighton, South Australia | over 60 | District |
| 1958 | Athens, Greece | 27 | Nursing staff |
| 1958-59 | South West London | 2 | District |
| 1959 | North West London | 7 | District |
| 1959 | Newcastle upon Tyne, England, | 48 | Student teachers |
| 1960 | Mississippi, USA | ? | District |
| 1961 | Illinois, USA | ? | District |
| 1961-62 | New York State | 26 | Convent |
| 1948-65 | Los Angeles, USA | approx. 330 (sporadic) | District |
| 1964-65 | Kentucky, USA | 59 | Factory and District |
| 1964-66 | North West London | approx. 370 | District |
| 1965-66 | Galveston County, Texas, USA | 55 | District |
| 1968 | Fnaidek, Lebanon | ? | ? |
| 1969-70 | Edinburgh, Scotland | 4 (sporadic) | District |
| 1970 | Great Ormond Street Hospital, London | over 145 | Hospital staff |
| 1970 | Lackland Air Force Base, Texas, USA | 221 | Hospital staff |
| 1975 | New York State, USA | ? | District |
| 1976 | South West Ireland | over 65 | District |
| 1977 | Dallas—Fort Worth, Texas, USA | ? | District |

Taken from Behan (1980)

Documented clusters of cases

| | | | |
|---|---|---|---|
| 1979 | Southampton (May et al. 1980) | 45 | School |
| 1980 -> | West Coast Scotland Ayr/Helensburgh (Fegan et al. 1983. Calder and Warnock 1984. | 22+38+ | GP Area |
| 1981 | Balfron (near Glasgow) (Keighley and Bell 1983) | 20 | GP Area |
| 1984 | Lake Tao, Nevada (Buchwald et al. 1992) | 90 | |
| -> | Truckee Levington, Nevada + Lake Tao (Levine 1992) | 250 | Area |
| 1984 | Montreal, Quebec, Ontario (Hyde 1992b) | 500 | Area |
| 1984 | N. Carolina Symphony Orchestra (Gruffman 1992) | 7 | Orchestra |
| 1985 | Lyndonville, New York (Bell et al. 1991) | 33 | School |
| 1988 | Glasgow College of Technology (Durndell 1988/1989) | 27+ | College |
| 1988 | Minnesota (Peterson et al. 1991) | 135 | Area |
| 1989 | Rosewall California (Hyde 1992b) | 11+ | Hospital |
| 1990 | Elgrove High School (Hyde 1992b) | | School |

## Appendix 1 Table 4. Cases of epidemic disease, to show spread.

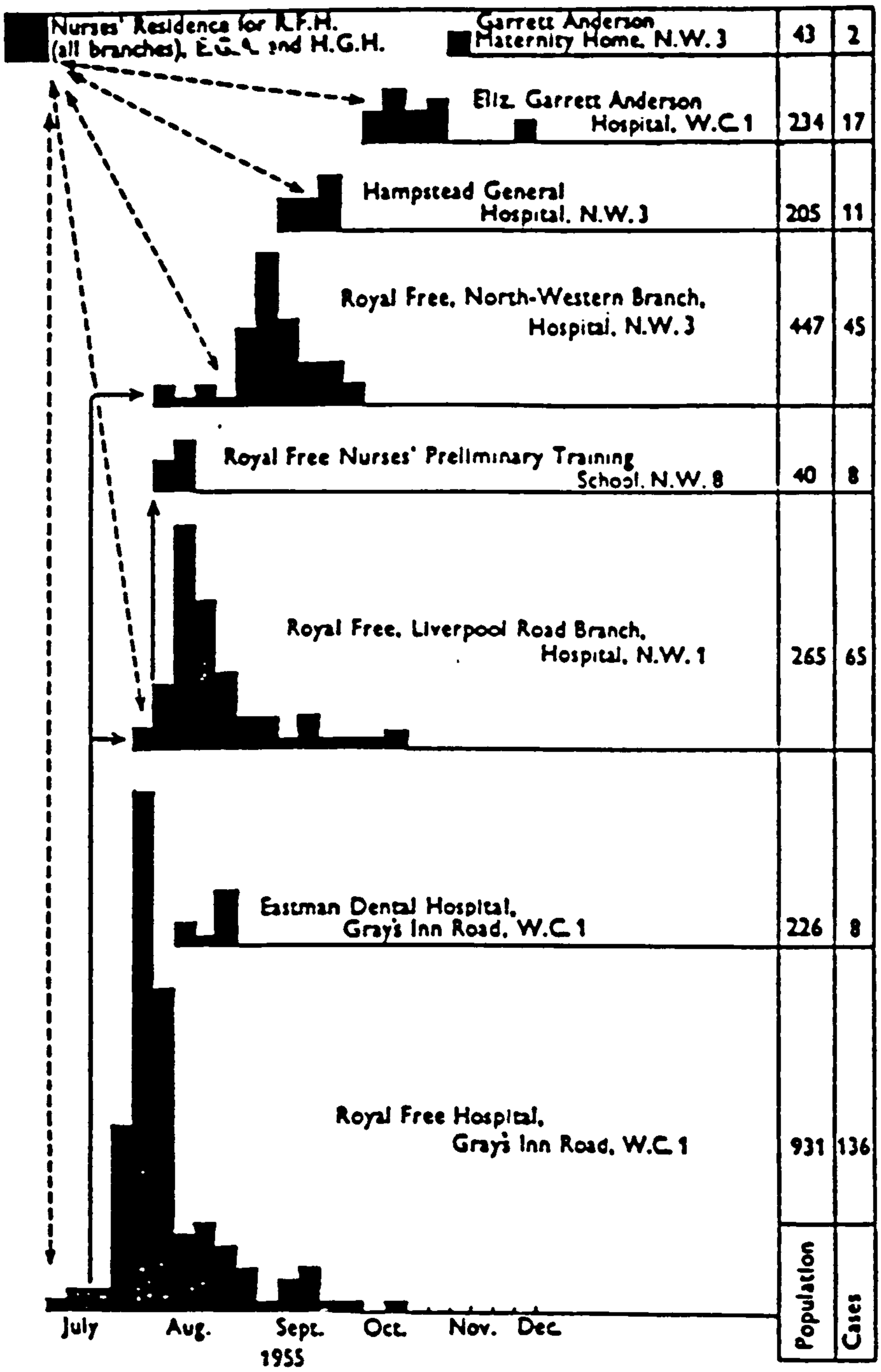



**Fig. 2. Cases of epidemic disease by hospital (dates of onset).**

Taken from Crowley, Nelson and Stovin 1957

## Appendix 1 Table 5. Apparent incubation period

| Date of exposure to first host | Date of onset second host | Apparent incubation period |
|---|---|---|
| 20. vii. 55 | 27. vii. 55 | 7 days |
| 16. vii. 55 | 22. vii. 55 | 6 days |
| 29. vii. 55 | 3. viii. 55 | 5 days |
| Before 28. xii. 55 | 1. i. 56 | Not less than 4 days |
| Before 23. vii. 55 | 27. vii. 55 | Not less than 4 days |
| Before 9. viii. 55 | 15. viii. 55 | Not less than 6 days |
| Before 17. viii. 55 | 21. viii. 55 | Not less than 4 days |

Taken from Crowley, Nelson and Stovin 1957

## Appendix 1 Table 6. Cerebrospinal-Fluid Abnormalities

| Location of outbreak | No. of persons examined | No. with abnormal CSF (pleocytosis) |
|---|---|---|
| California | 59 | 3 |
| Wisconsin | 2 | 0 |
| England | 1 | 0 |
| Iceland | 8 | 5 |
| Australia | 59 | 5 |
| Kentucky | 3 | 0 |
| New York | 11 | 2 |
| Denmark | 5 | 0 |
| London, England | 6 | 0 |
| Coventry, England | 9 | 0 |
| Maryland | 25 | 0 |
| Tallahassee, Florida | 101 | 7 |
| Germany | 7 | 0 |
| London, England | 18 | 0 |
| Punta Gorda, Florida | 5 | 0 |
| Coventry, England | 7 | 0 |
| Greece | 4 | 0 |

Taken from Henderson and Shelokor 1959

**Appendix 1 Table 7. Neurological signs in CFS**

| | No. of cases with objective neurological disorder | | | No. of cases without objective neurological disorder |
|---|---|---|---|---|
| | Severe | Moderate | Mild | |
| Changes in mononuclear series of white cells | 20 | 72 | 69 | 112 |

Taken from Crowley, Nelson and Stovin 1957

## Appendix 1 Table 8. Viruses Implicated in CFS

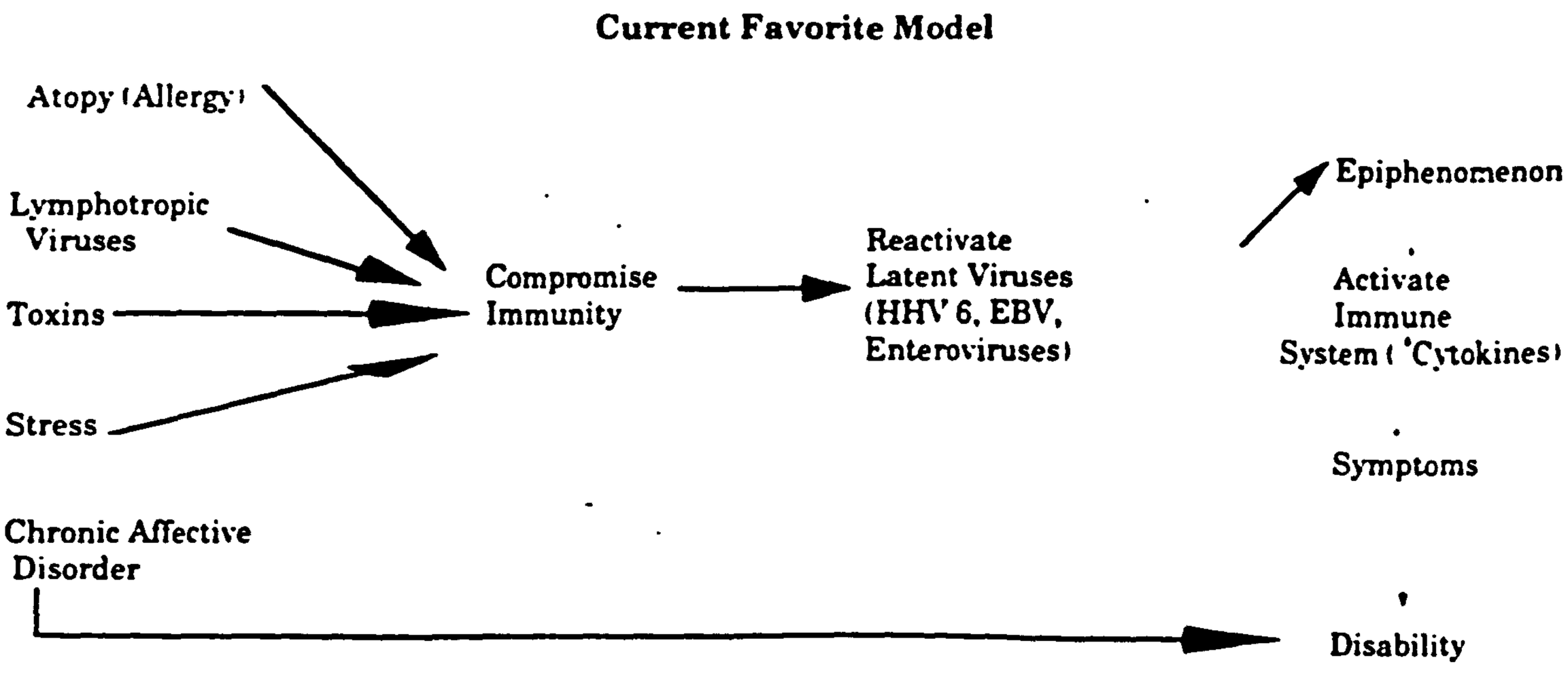
| | Los Angeles | Iceland | Adelaide | New York State | Middlesex Hospital | Copenhagen | Coventry Hospital |
|---|---|---|---|---|---|---|---|
| A.P.C. virus | | | | | | | |
| Brucellosis | | | | | | | |
| Coxsackie | | | | 0 (17) | | | |
| Encephalitis Eastern Equine | Nil | 0 (12) | | | | Nil | |
| Encephalitis Japanese B | Nil | 0 (12) | | | | Nil | |
| Encephalitis Western Equine | | 0 (12) | | | | | |
| Encephalitis St. Louis | | 0 (12) | | | | | |
| Encephalo-myocarditis | | | 0 (5) | | | | 0 (10) |
| Herpes Simplex | | | | | | | |
| Influenza A | | 0 (12) | | | | | |
| Influenza B | | | | | | | |
| Influenza C | | | | | | | |
| Leptospirosis | | | 0 (5) | | 0 (8) | | 0 (10) |
| Louping Ill | | | | | | | |
| Lymphocytic Choriomeningitis | | 0 (12) | 0 (5) | | 0 (8) | | 0 (10) |
| Mumps | | | 0 (5) | | * (8) | | * (10) |
| Paracolon (Bethesda-Ballerup) | | | | | | | |
| Polio Virus | | | 0 (5) | 0 (17) | 3† (10) | | 0 (10) |
| Psittacosis | | | | | | | |
| Q. Fever | | 0 (12) | | | | | |
| Rabies | | 0 (12) | | | | | |
| Rickettsia Burneti | | | | | | | |
| Toxoplasmosis | | | | | | | |

| | Bethesda Hospital | Seward, Alaska | Berlin | Durban Hospital | Royal Free Hospital (1) | Punta Gorda | Royal Free Hospital (2) |
|---|---|---|---|---|---|---|---|
| A.P.C. virus | 0 (7) | | | | 0 (?) | | |
| Brucellosis | † (13) | | 0 (7) | | | 0 (12) | |
| Coxsackie | 0 (5) | | | | | | |
| Encephalitis Eastern Equine | | | | No | | 0 (12) | |
| Encephalitis Japanese B | | | | details | | | Nil |
| Encephalitis Western Equine | | | | known | | 0 (12) | |
| Encephalitis St. Louis | | | | | | 0 (12) | |
| Encephalo-myocarditis | | | | | 0 (6) | | |
| Herpes Simplex | | | | | 0 (?) | | |
| Influenza A | | | 0 (7) | | 0 (?) | | |
| Influenza B | | | 0 (7) | | 0 (?) | | |
| Influenza C | | | | | 0 (?) | | |
| Leptospirosis | | | | | 0 (?) | 0 (12) | |
| Louping Ill | | | | | 0 (?) | | |
| Lymphocytic Choriomeningitis | | | | | | 0 (12) | |
| Mumps | | | | | 0 (?) | * (12) | |
| Paracolon (Bethesda-Ballerup) | See text | | | | 0 (12) | | |
| Polio Virus | | † (19) | | | | | |
| Psittacosis | | | | | 0 (?) | | |
| Q. Fever | | | | | | | |
| Rabies | | | | | | | |
| Rickettsia Burneti | | | | | 0 (?) | | |
| Toxoplasmosis | | | | | 0 (?) | | |

*Note: Figures indicate number of positive tests; in parentheses, number of cases studied. * Immune bodies in titres suggesting remote infection found in some cases. † The findings were of doubtful significance and are discussed in the text.*

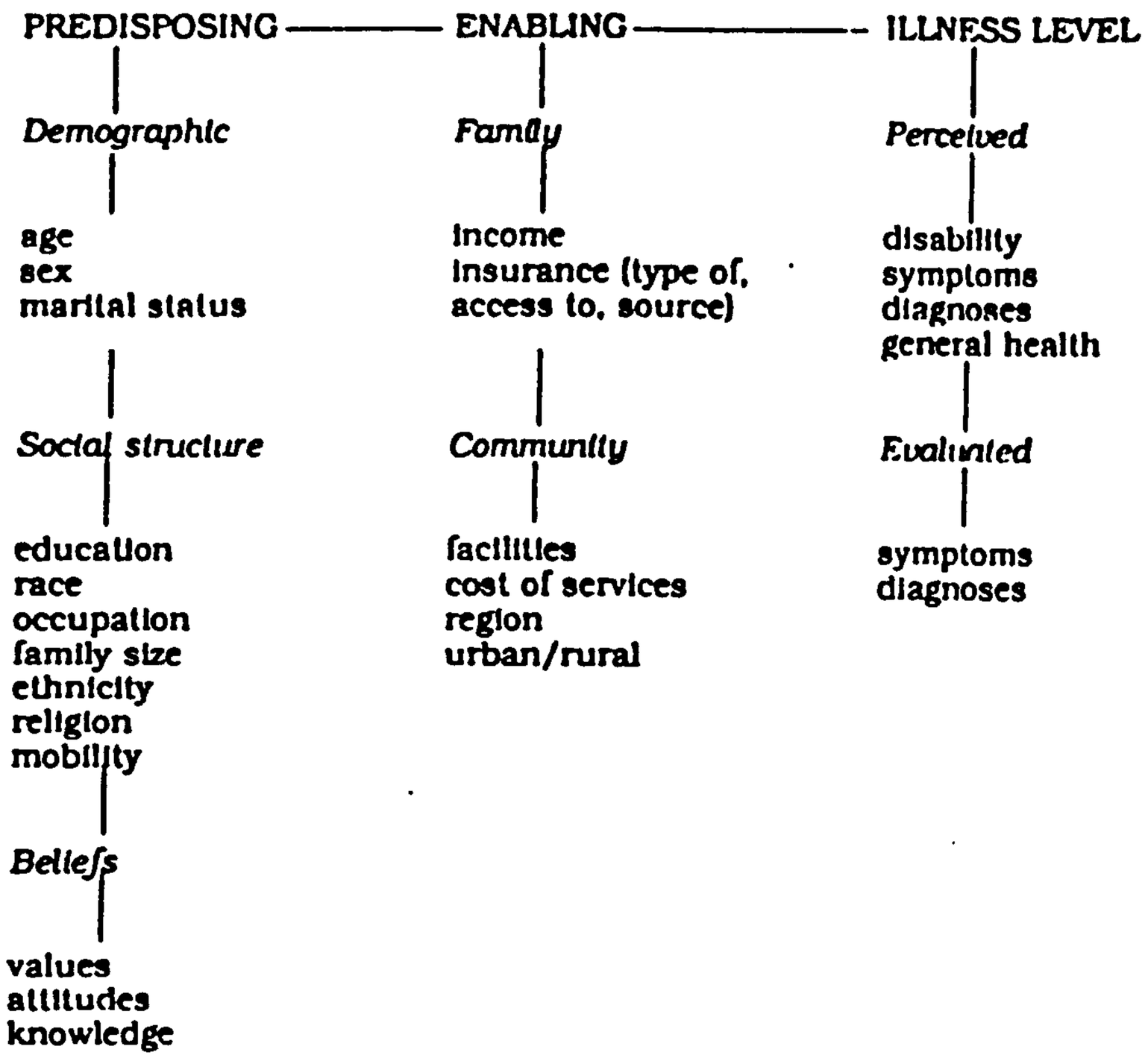
Taken from Acheson 1992

## Appendix 1 Table 9. Model for the pathogenesis of CFS



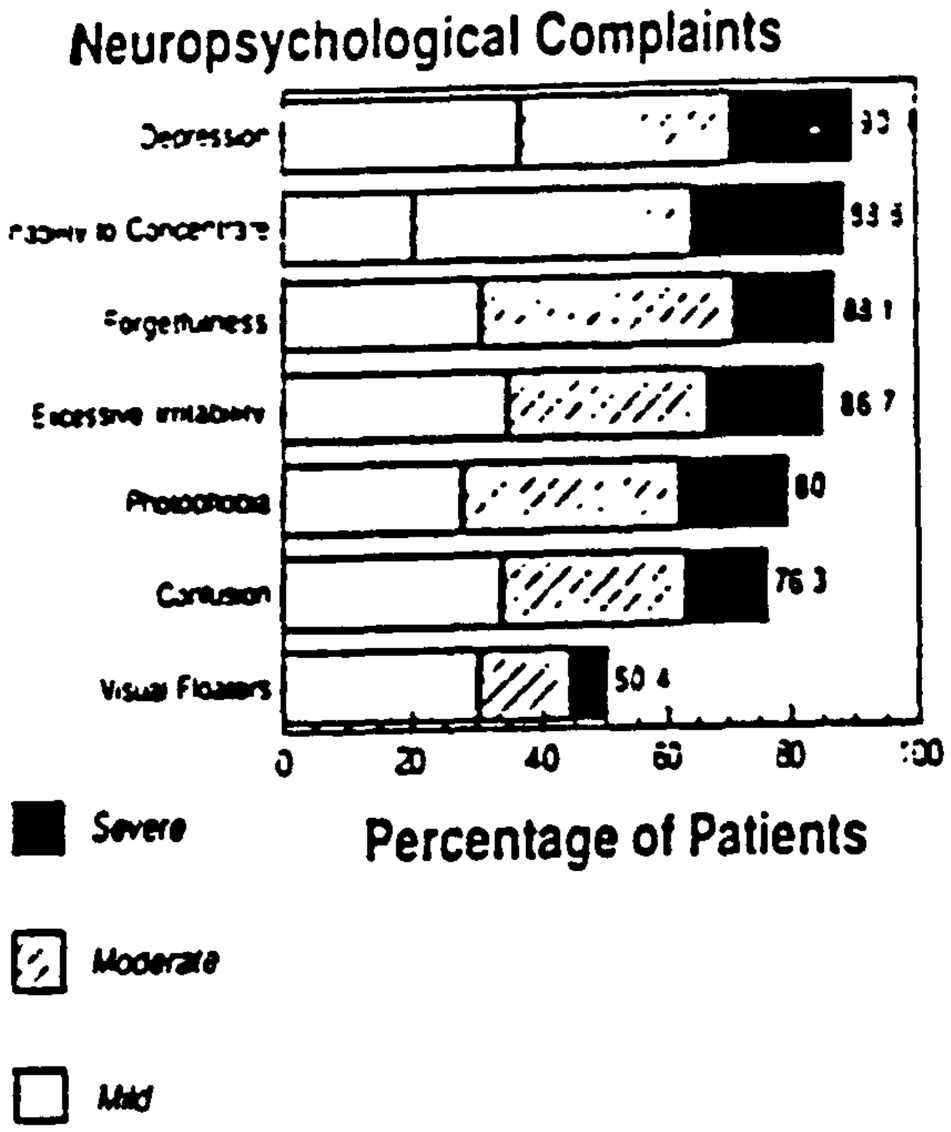

Taken from Komaroff 1992.

## Appendix 1 Table 10. Individual determinants of health service utilization, according to the Anderson model




Taken from Williams, Wilkinson and Arreghini 1990

## Appendix 1 Table 11. Severity of neuropsychological complaints in 135 CFS patients




Taken from Peterson, Schenck and Sherman 1991

## Appendix 1 Table 12. Diagnosis of MS

| Signs and Symptoms of Multiple Sclerosis in 1271 Patients* | | |
|---|---|---|
| Site and type of involvement | Initially % | Total course % |
| Pareses | 42.9 | 87.6 |
| Sensory changes | 40.7 | 87.0 |
| Visual alterations | 35.9 | 66.1 |
| Cerebral symptoms | 31.0 | 39.2 |
| Brainstem &/or cerebellar signs | 22.5 | 81.6 |
| Spasticity &/or Babinski sign | 19.4 | 85.1 |
| Diplopia | 12.7 | 33.9 |
| Sphincter &/or sexual dysfunction | 9.6 | 63.2 |
| Fifth &/or seventh cranial nerve | 6.9 | 23.1 |

*: Adapted from Bauer[1]

| Signs and Symptoms in 157 Cases of Autopsy-Proven Multiple Sclerosis* | |
|---|---|
| SIGNS | % |
| Spasticity and/or hyperreflexia | 98 |
| Babinski sign | 92 |
| Absent abdominal reflexes | 82 |
| Dysmetria or intention tremor | 79 |
| Nystagmus | 71 |
| Impairment of vibratory sensation | 61 |
| Impairment of position sensation | 52 |
| SYMPTOMS | % |
| Muscle weakness | 96 |
| Ocular problems (altered vision or diplopia) | 85 |
| Urinary disturbance | 82 |
| Gait ataxia | 60 |
| Paresthesiae | 60 |
| Dysarthria or scanning speech | 54 |

* Modified from Poser et al[2]

Taken from Poser 1992

## Appendix 1 Table 13. Frequency of psychiatric dysfunction

**Frequency of Psychiatric Dysfunction in Adults**

| Author | Assessment Used | Psychiatric Disorder in CFS | | Psychiatric Disorder in Controls | |
|---|---|---|---|---|---|
| | | Current | Lifetime | Current | Lifetime |
| Manu (56,57) | DIS | 59% | 77% | NA | NA |
| Kruesi (58) | DIS | NA | 75% | NA | NA |
| Wessely (59) | SADS | 72% | NA | 36% | NA |
| Taerk (60) | DIS | 67% | NA | NA | 29% |
| Katon (61) | DIS | 45% | 86% | 6% | 48% |

DIS - National Institute of Mental Health (NIMH) Diagnostic Interview Schedule
SADS - Schedule for Affective Disorders and Schizophrenia

Taken from Buchwald 1992

# APPENDIX 2

# METHODOLOGY TEST ITEMS

## Appendix 2 Item 1. General Questionnaires

This Appendix contains the various versions of the general questionnaire used. The questions are the same, except that some questions were not relevant for all groups, and therefore were excluded. Filling in the questionnaire was assisted by the experimentor.

The versions contained in this Appendix are as follows:

Item 1(a) General questionnaire for CFS patients
Item 1(b) General questionnaire for Crohns/colitis patients
Item 1(c) General questionnaire for Normal controls
Item 1(d) General questionnaire for CFS and Crohns/colitis patients: second testing
Item 1(e) General questionnaire for normal controls: second testing

## Appendix 2 Item 1(a). General questionnaire for CFS patients

| | Tick |
|---|---|
| When do you think you started to be ill with ME? | ☐ |
| When were you diagnosed as having ME? | ☐ |
| Was this by a GP or a Consultant? State medical department if Consultant. | ☐ |
| Are you taking any medical drugs? | ☐ |
| Do you think you are getting better? | ☐ |
| Are you working? | ☐ |
| What was your job prior to being ill? | ☐ |
| Were you ill to begin with, with any specific illness? | ☐ |
| Did you have or were you suspected of having encephalitis? | ☐ |
| Did you have an initial illness which was much worse than having bad flu? | ☐ |
| In the two years before you were ill with ME, how was your health? | ☐ |
| Did you have a lot of antibiotics? | ☐ |
| Have you had any other serious illness? Psychiatric treatment? prior to having ME? | ☐ |
| Did you have contact with anyone else with ME? | |
| AT WORK VERY FREQUENT CONTACT | ☐ |
| FAMILY VERY FREQUENT CONTACT | ☐ |
| Did you have contact with anyone with Coxsackie B, Glandular Fever, or other major viral illness at the time? Specify. | ☐ |
| Did or does anyone else you are in close contact with suffer from similar symptoms? What is their relationship with you? Work Family etc. | ☐ |
| What leisure activities did you take part in before were ill? LIST | |
| How many times a week did you do each activity and for how long? | ☐ |
| Have you every won any medals or important races for sport? Specify Year. | ☐ |
| Have you ever competed for a sports club or at borough, area, national or international level? | ☐ |

| | Tick |
|---|---|
| When you were working before you were ill was your job physically active? | ☐ |
| Did you have to do a lot of walking? | ☐ |
| Did you have to stand for long periods of time? | ☐ |
| Did your work involve studying? No. of hours per week av. | ☐ |

In the 18 months before having ME did any of the following happen to you?

| | |
|---|---|
| Were you working for some particular exams? Specify. | ☐ |
| Were you married/divorced/widowed/your partner pregnant/have a new baby in the house/adopted a child/grandchildren? | ☐ |
| Did you move area/house? | ☐ |
| Has any of your family been ill? | ☐ |
| Have you been bereaved? | ☐ |
| Did you or your spouse lose or change job? Specify. | ☐ |
| Were you involved in any accident/fore/robbery or other particularly stressful situation? | ☐ |
| Have you found the medical profession helpful? Sympathetic? during this illness? | ☐ |
| Do you do any of your previous leisure activities? | ☐ |
| Do you have any particular activities that you do when you are unwell eg. reading? TV? Radio? | ☐ |
| Do you do household chores? Most Some A few None | ☐ |
| Do you manage to hoover? Carry and hand up wet washing? most of the time? | ☐ |
| Are there any things that you can do now that you could not do 6 months ago? Specify. | ☐ |
| Do you feel depressed or anxious? More than 6 months ago? | ☐ |
| Do you have any particular goals within the next 6 months? Specify. Realistic | ☐ |
| How long do you think it will take you to get reasonably well? | ☐ |
| Do you feel you are coping/not coping well with having ME? | ☐ |
| Which of these do you feel is worse than ME - Arthritis, Stomach ulcers, Angina, Poor hearing, Broken leg, Cancer, Multiple sclerosis? | ☐ |

## Appendix 2 Item 1(b). General questionnaire for Crohns/colitis patients

Date of Birth

Tel No

When did you start to be ill? When did you receive a diagnosis?

Do you think you are getting better?

In the two years before your illness how was your health?
Did you have to take a lot of antibiotics for anything?

Have you had any serious illness (Specify), psychiatric treatment, epilepsy, head injury, or a history of alchohol or drug abuse?

Are you taking any medical drugs?

Do you drink alchohol? how much per week?

Do you have contact with anyone who has Myalgic Encephalomyelitis/ Post Viral Fatigue Syndrome or coxsakie B or glandular fever?

Are you working? What is your job? Is your job physically active?
Do you have to do a lot of walking?
Do you have to stand for long periods of time?
Does your work involve studying ? No of hours per week?

Do you have any problems with following TV or radio programmes or reading?

Do you do household chores Most Some A few None

What were are your leisure activities prior to your illness? Specify what and how many hours per week.
Do you still do these activities? Specify what and how many hours per week.

Have you ever won medals or important races for sport or competed at club, borough national or international level?

In the last 18 months has any of these happenned to you?

Have you been working for any particular exams?
Have you been married/divorced you or partner pregnant/ have a new baby/ adopted a child /had grandchildren ?
Have you moved area/house ?
Have you been bereaved or had a serious illness in the family?
Have you or partner lost or chasnged job?
Have you been involved in any other particularly stressful situation ? eg fire/accident/ robbery

## Appendix 2 Item 1(b) continued

Have you found the medical profcssion helpful? Sympathetic? during the illness

Do you have any expectations as to how long it might take to get reasonably well?

Do you feel depressed or anxious ?

Do you have any particular goals in the next six months? Specify

Do you feel you are coping/not coping with having chronic inflamatory bowel disease?
Which of these do you think is worse than Chronic Inflamatory Bowel Disease
Arthritis
Angina
Permanent slight poor hearing
Broken leg
Multiple Sclerosis
Cancer
ME

## Appendix 2 Item 1(c). General questionnaire for Normal controls

Date of Birth

Tel No

Have you had any serious illness (Specify), psychiatric treatment, epilepsy, head injury, or a history of alchohol or drug abuse?

In the last two years how has your health been?

Did you have to take a lot of antibiotics for anything?

Are you taking any medical drugs?

Do you drink alchohol? how much per week?

Do you have contact with anyone who has Myalgic Encephalomyelitis/ Post Viral Fatigue Syndrome or coxsakie B or glandular fever?

Are you working? What is your job? Is your job physically active?

Do you have to do a lot of walking?
Do you have to stand for long periods of time?
Does your work involve studying ? No of hours per week?

Do you have any problems with following TV or radio programmes or reading?

Do you do household chores Most Some A few None

What are your leisure activities?
Specify what and how many hours per week.

Have you ever won medals or important races for sport or competed at club, borough national or international level?

In the last 18 months has any of these happenned to you?

Have you been working for any particular exams?
Have you been married/divorced you or partner pregnant/ have a new baby/ adopted a child /had grandchildren ?
Have you moved area/house ?
Have you been bereaved or had a serious illness in the family?
Have you or partner lost or chasnged job?
Have you been involved in any other particularly stressful situation ? eg fire/accident/ robbery

Do you feel depressed or anxious ?

Do you have any particular goals in the next six months? Specify

Which of these do you think is worse than Myalgic Encephalomyelitis
Arthritis
Stomach Ulcers
Angina
Permanent slight poor hearing
Broken leg
Multiple Sclerosis
Cancer

Appendix 2 Item 1(d). General questionnaire for CFS and Crohns/colitis patients: second testing

ME Questionnaire: PVFS/chronic Second Testing

Date of Birth

Tel No

Are you taking any medical drugs?

Do you drink alcohol? how much per week?

Do you have contact with anyone who has Myalgic Encephalomyelitis / Post Viral Fatigue Syndrome or Coxsackie B or glandular fever?

Are you working? What is your job?

Do you have problems with following TV or radio programmes or reading?

Do you do household chores Most Some A few None

Leisure activities:- Specify what and how many hours per week.

Do you feel depressed or anxious? more or less than when you last saw me?

Do you have any particular goals in the next six months? Specify.

Do you have any expectations as to when you might recover fully?

Do you feel you are coping / not coping with the illness?

Appendix 2 Item 1(e). General questionnaire for normal controls: second testing

ME Questionnaire: Controls Second Testing

Date of Birth

Tel No

Are you taking any medical drugs? Specify.

Do you drink alcohol? how much per week?

Do you have contact with anyone who has Myalgic Encephalomyelitis / Post Viral Fatigue Syndrome or Coxsackie B or glandular fever?

Are you working? What is your job?

Do you have problems with following TV or radio programmes or reading?

Do you do household chores Most Some A few None

What are your leisure activities?

Specify what and how many hours per week.

Do you feel depressed or anxious? more or less than when you last saw me?

Do you have any particular goals in the next six months? Specify.

## Appendix 2 Item 2(a). Consent form and explanation

You have been asked to take part in a research study in Post Viral Fatigue Syndrome.

The purpose of the study is:-

(a) To find out how memory and concentration improves during recovery from Post Viral Fatigue Syndrome.

(b) To compare psychological factors, for example, mood, attitude to and perception during the illness of Post Viral Fatigue Syndrome sufferers to other patients with chronic illness.

What would you have to do:-

(a) You would need to attend the Clinic (usually on a day when you would be seeing the doctor) normally either for 1½ hours ~~or for two, ½ hour sessions~~.

(b) You would be asked to do some short tests of reaction time, memory and concentration, and fill in some questionnaires.

(c) You would be asked to come back 4 months later to re-do some of the tests (a shorter session - about 1 hour).

Your help would be greatly appreciated.

Appendix 2 Item 2(a) continued

# C O N S E N T  F O R M

I _____ (full name and address)

_____

_____

_____

_____

freely and voluntarily consent to take part in a clinical research study on

_____

_____

_____

which so far as is known should not carry any risk.

I have read the accompanying information sheet. The nature and purpose of the study has been explained to me by Dr. _____.

I have had the opportunity to ask any questions and I understand fully what is proposed.

I recognise that I may receive no benefit personally from the study.

I understand that I am free to withdraw my consent at any time without prejudice to me or my medical care. I have been assured that any information obtained from me will not be disclosed to any other party in a manner which will reveal my identity.

Signature _____ Date _____

I confirm that I/Dr. _____ have/has explained the nature and purpose of the clinical research study and the procedure in respect of which consent has been given by the above named.

Signature_____ Date _____

Appendix 2 Item 2(b)

You have been asked to take part in a research study, into Myalgic Encephalomyelitis, as a normal subject.

The purpose of this study is:-

To compare your performance with that of patients with Post Viral Fatigue Syndrome (PVFS or Myalgic Encephalomyelitis); to find out if patients with PVFS suffer from a deterioration in memory and concentration which cannot be accounted for by psychological factors.

What would you have to do:-

a) You would be asked to come to St. Andrew Ambulance Headquarters / Ruchill Hospital session of 1 to 1 and a quarter hours.

b) You would be asked to do some short tests of memory, reaction time and concentration, and to fill in some questionnaires.

c) You would be asked to come back 4-6 months later to re-do some of the tests (lasting approximately 1 hour).

## Appendix 2 Item 2(c)

You have been asked to take part in a research study.

The purpose of the study is:-

To compare aspects of your illness with that of Post-Viral Fatigue Syndrome or Myalgic Encephalomyelitis.

To find out if patients with Post Viral Fatigue Syndrome suffer a greater degree of depression, different attitude to illness or more problems with memory and attention than patients with other illnesses of comparable duration and severity.

What would you have to do:-

a) You would be asked to attend the Clinic - (normally on a day you would be seeing the doctor) either for 1½ hours ~~or for two, ¾ hour sessions.~~

b) You would be asked to do some short tests of memory, reaction time and concentration, and fill in some questionnaires.

c) You would be asked to come back 4 months later to re-do some of the tests (lasting approximately 1 hour).

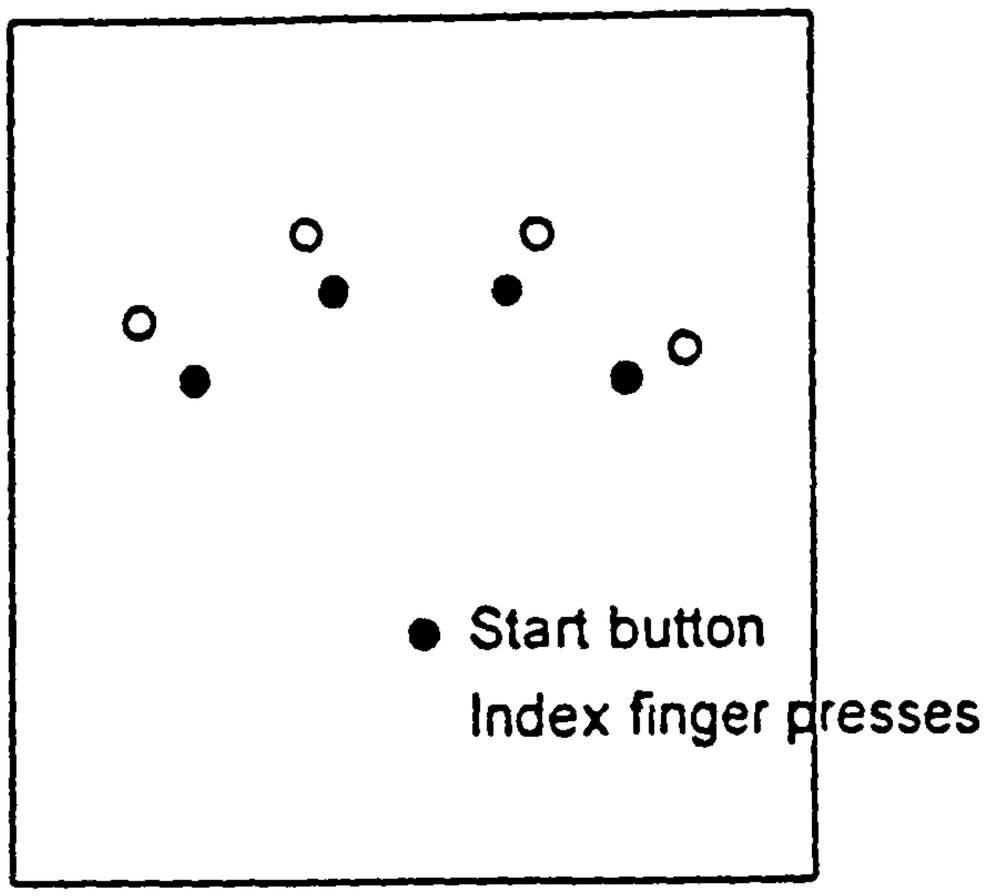
Your assistance would be greatly appreciated to help us learn more about a puzzling illness which has affected this part of Scotland.

## Appendix 2 Item 3. Weschler Form 1 - Scottish Version

Logical Memory.

Anna Thompson/ of East/ Kilbride/ employed/ as a cleaner/ in an office block/ reported/ at the central/ police station/ that she had been held up/ on Sauchiehall Street/ the night before/ and robbed/ of fifteen pounds/. She had four/ little children/ the rent/ was due/ and they had not eaten/ for two days/. The officers/ touched by the woman's story/ made a collection/ for her/.

## Appendix 2 Item 4. Layout of Reaction Time box




Key

o light

● finger button

## Appendix 2 Item 5. Scored CES-D form

CES-D Scale Scoring.

Circle the number for each statement which best describes how often you felt or behaved this way—DURING THE PAST WEEK.

| DURING THE PAST WEEK: | Rarely or None of the Time (Less than 1 Day) | Some or a Little of the Time (1-2 Days) | Occasionally or a Moderate Amount of Time (3-4 Days) | Most or All of the Time (5-7 Days) |
|---|---|---|---|---|
| | | Item Weights | | |
| 1. I was bothered by things that usually don't bother me | 0 | 1 | 2 | 3 |
| 2. I did not feel like eating; my appetite was poor | 0 | 1 | 2 | 3 |
| 3. I felt that I could not shake off the blues even with help from my family or friends | 0 | 1 | 2 | 3 |
| 4. I felt that I was just as good as other people | 3 | 2 | 1 | 0 |
| 5. I had trouble keeping my mind on what I was doing | 0 | 1 | 2 | 3 |
| 6. I felt depressed. | 0 | 1 | 2 | 3 |
| 7. I felt that everything I did was an effort | 0 | 1 | 2 | 3 |
| 8. I felt hopeful about the future | 3 | 2 | 1 | 0 |
| 9. I thought my life had been a failure | 0 | 1 | 2 | 3 |
| 10. I felt fearful | 0 | 1 | 2 | 3 |
| 11. My sleep was restless | 0 | 1 | 2 | 3 |
| 12. I was happy | 3 | 2 | 1 | 0 |
| 13. I talked less than usual | 0 | 1 | 2 | 3 |
| 14. I felt lonely | 0 | 1 | 2 | 3 |
| 15. People were unfriendly | 0 | 1 | 2 | 3 |
| 16. I enjoyed life | 3 | 2 | 1 | 0 |
| 17. I had crying spells | 0 | 1 | 2 | 3 |
| 18. I felt sad | 0 | 1 | 2 | 3 |
| 19. I felt that people disliked me | 0 | 1 | 2 | 3 |
| 20. I could not get "going" | 0 | 1 | 2 | 3 |

Score is sum of 20 endorsed item weights.
Possible range: 0-60

## Appendix 2 Item 6. WAIS blocks diagram of patterns

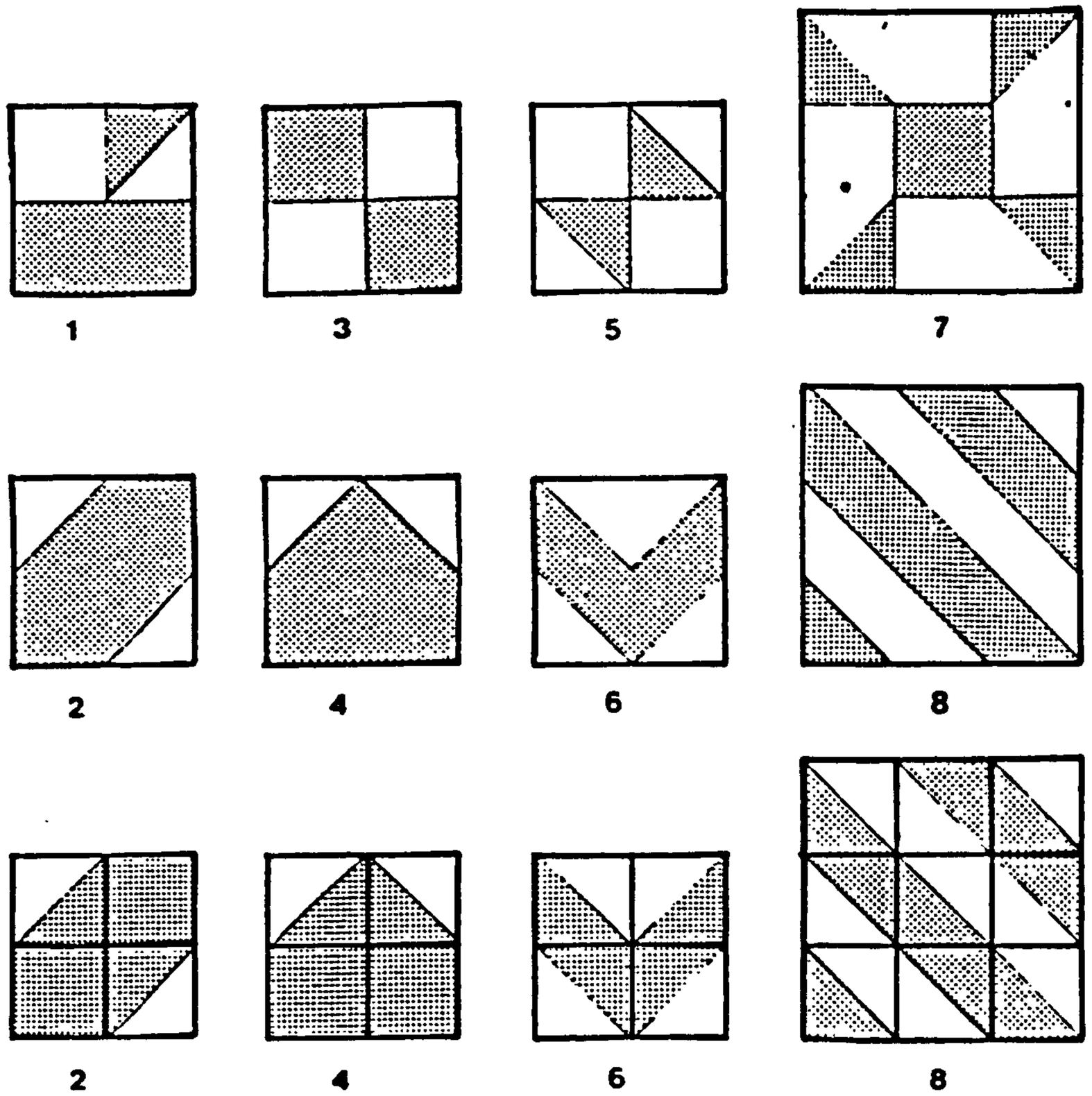



**Fig. 1.1** Non embedded and embedded items from the WAIS Block Design sub-test.

From Walsh 1985

## Appendix 2 Item 7. Symptom data form

| Please mark if you have had any of these symptoms<br>1 = Mild 2 = Moderate 3 = Severe | THIS WEEK | NOW |
|---|---|---|
| Headache | | |
| Muscle pain | | |
| Neck pain | | |
| Sore eyes | | |
| Sensitivity to light | | |
| Excessive fatigue | | |
| Difficulty standing | | |
| Pins and needles or numbness | | |
| Giddiness/Dizziness | | |
| Muscle twitching | | |
| Shivering attacks | | |
| Sickness/Vomiting | | |
| Spontaneous bruising | | |
| Stiff neck | | |
| Pain in abdomen | | |
| Fainting | | |
| Diarrhoea/Constipation | | |
| Blurred vision | | |
| Palpitations | | |
| Abdominal distension | | |
| Sore throat | | |
| Pain in chest | | |
| Tremor | | |
| Noise in ears | | |
| Frequent crying | | |
| Nightmares | | |
| Speech difficulties | | |
| Rash or irritation of the skin | | |
| Painful joints | | |
| Earache | | |
| Deafness | | |
| Seeing double | | |
| Cough | | |
| Frequency or difficulty passing urine | | |
| Dryness in the mouth | | |
| Flushing | | |
| Sweating unduly | | |
| Panic feelings | | |
| Guilt feelings | | |

| | THIS WEEK | NOW |
|---|---|---|
| Bad taste in mouth | | |
| 'Indigestion' | | |
| Loss of appetite | | |
| Depression | | |
| Insomnia | | |
| Felt memory/concentration impaired | | |
| Increased thirst | | |

Please indicate along the line how active you feel.

Exhausted — Energetic

## Appendix 2 Item 8. Beliefs about illness scales

POST VIRAL FATIGUE SYNDROME/CFS/ME

| | | |
|---|---|---|
| Most people never recover. | ⊥⊥⊥⊥⊥⊥⊥ | Most people recover completely. |
| I have a big chance of getting it. | ⊥⊥⊥⊥⊥⊥⊥ | I have no chance of getting it. |
| Scares most people A very powerful disease. | ⊥⊥⊥⊥⊥⊥⊥ | Scares hardly anybody A very mild disease. |
| Very well understood by doctors. | ⊥⊥⊥⊥⊥⊥⊥ | Hardly anything is known about it. |
| Many people get it | ⊥⊥⊥⊥⊥⊥⊥ | Almost nobody gets it. |

CANCER

| | | |
|---|---|---|
| Most people never recover. | ⊥⊥⊥⊥⊥⊥⊥ | Most people recover completely. |
| I have a big chance of getting it. | ⊥⊥⊥⊥⊥⊥⊥ | I have no chance of getting it. |
| Scares most people A very powerful disease. | ⊥⊥⊥⊥⊥⊥⊥ | Scares hardly anybody A very mild disease. |
| Very well understood by doctors. | ⊥⊥⊥⊥⊥⊥⊥ | Hardly anything is known about it. |
| Many people get it. | ⊥⊥⊥⊥⊥⊥⊥ | Almost nobody gets it. |

BROKEN LEG

| | | |
|---|---|---|
| Most people never recover. | ⊥⊥⊥⊥⊥⊥⊥ | Most people recover completely. |
| I have a big chance of getting it. | ⊥⊥⊥⊥⊥⊥⊥ | I have no chance of getting it. |
| Scares most people A very powerful disease. | ⊥⊥⊥⊥⊥⊥⊥ | Scares hardly anybody A very mild disease. |
| Very well understood by doctors. | ⊥⊥⊥⊥⊥⊥⊥ | Hardly anything is known about it. |
| Many people get it. | ⊥⊥⊥⊥⊥⊥⊥ | Almost nobody gets it. |

ARTHRITIS

| | | |
|---|---|---|
| Most people never recover. | _\|_\|_\|_\|_\|_\|_\|_\| | Most people recover completely. |
| I have a big chance of getting it. | _\|_\|_\|_\|_\|_\|_\|_\| | I have no chance of getting it. |
| Scares most people A very powerful disease. | _\|_\|_\|_\|_\|_\|_\|_\| | Scares hardly anybody A very mild disease. |
| Very well understood by doctors. | _\|_\|_\|_\|_\|_\|_\|_\| | Hardly anything is known about it. |
| Many people get it. | _\|_\|_\|_\|_\|_\|_\|_\| | Almost nobody gets it. |

MULTIPLE SCLEROSIS

| | | |
|---|---|---|
| Most people never recover. | _\|_\|_\|_\|_\|_\|_\|_\| | Most people recover completely. |
| I have a big chance of getting it. | _\|_\|_\|_\|_\|_\|_\|_\| | I have no chance of getting it. |
| Scares most people A very powerful disease. | _\|_\|_\|_\|_\|_\|_\|_\| | Scares hardly anybody A very mild disease. |
| Very well understood by doctors. | _\|_\|_\|_\|_\|_\|_\|_\| | Hardly anything is known about it. |
| Many people get it. | _\|_\|_\|_\|_\|_\|_\|_\| | Almost nobody gets it. |

STOMACH ULCERS

| | | |
|---|---|---|
| Most people never recover. | _\|_\|_\|_\|_\|_\|_\|_\| | Most people recover completely. |
| I have a big chance of getting it. | _\|_\|_\|_\|_\|_\|_\|_\| | I have no chance of getting it. |
| Scares most people A very powerful disease. | _\|_\|_\|_\|_\|_\|_\|_\| | Scares hardly anybody A very mild disease. |
| Very well understood by doctors. | _\|_\|_\|_\|_\|_\|_\|_\| | Hardly anything is known about it. |
| Many people get it. | _\|_\|_\|_\|_\|_\|_\|_\| | Almost nobody gets it. |

## Appendix 2 Item 9. Checklist

PATIENT'S NAME .....

PVFS/CHRONIC/NORMAL

INTRODUCTION

EXPLANATORY LETTER ☐

CONSENT FORM ☐

QUESTIONNAIRE ☐

NART ☐

COMPUTER

REACTION TIME ☐

THRESHOLD ☐

VISUAL MEMORY ☐

MEMORY TESTS

WESCHLER BACK ☐

FRONT ☐

WORD RECOG. ☐

REY DRAW ☐

MEM ☐

TIMED TESTS

WORD FLUENCY ☐

FINGER TAPPING ☐

WAIS BLOCKS ☐

SYMBOL CODE ☐

STROOP ☐

PASAT ☐

QUESTIONNAIRES - 1

SPEILBURGER ☐

CDES ☐

FATIGUE SCALE ☐

SYMPTOM LIST ☐

QUESTIONNAIRES - 2

DAS ☐

HEALTH L.O.C. ☐

ILLNESS BELIEF ☐

MHQ ☐

## Appendix 2 Item 10. Copy of Stroop card

1 BLACK RED WHITE RED BLUE

2 BLUE WHITE BLACK RED WHITE

3 WHITE BLACK BLUE BLUE RED

4 BLACK RED WHITE BLUE RED

5 WHITE BLACK BLUE BLACK RED

6 RED BLUE BLACK WHITE BLUE

7 WHITE BLACK RED BLUE RED

8 BLACK WHITE BLUE RED BLUE

9 BLUE BLACK RED WHITE WHITE

10 BLACK WHITE BLACK RED BLUE

11 BLUE WHITE BLUE BLACK RED

12 WHITE BLACK WHITE RED BLUE

13 BLACK WHITE RED BLACK WHITE

14 RED WHITE BLUE WHITE BLACK

15 BLUE RED BLUE BLACK BLUE

16 RED RED BLACK BLACK WHITE

## Appendix 2 Item 11. Spielberger State/Trait Anxiety scale X questionnaire

# SELF-EVALUATION QUESTIONNAIRE

Developed by C. D. Spielberger, R. L. Gorsuch and R. Lushene

**STAI FORM X-1**

NAME _____ DATE _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *feel* right now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

| | NOT AT ALL | SOMEWHAT | MODERATELY SO | VERY MUCH SO |
|---|---|---|---|---|
| 1. I feel calm | ① | ② | ③ | ④ |
| 2. I feel secure | ① | ② | ③ | ④ |
| 3. | | | | |
| 4. | | | | |
| 5. | | | | |
| 6. | | | | |
| 7. | | | | |
| 8. | | | | |
| 9. | | | | |
| 10. | | | | |
| 11. | | | | |
| 12. | | | | |
| 13. | | | | |
| 14. | | | | |
| 15. | | | | |
| 16. | | | | |
| 17. | | | | |
| 18. | | | | |
| 19. | | | | |
| 20. | | | | |



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## SELF-EVALUATION QUESTIONNAIRE

### STAI FORM X-2

NAME _____ DATE _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

| | ALMOST NEVER | SOMETIMES | OFTEN | ALMOST ALWAYS |
|---|---|---|---|---|
| 21. I feel pleasant | ① | ② | ③ | ④ |
| 22. I tire quickly | ① | ② | ③ | ④ |
| | | | | |
| [illegible] interests | ① | ② | ③ | ④ |

## Appendix 2 Item 12. Health Locus of Control form B questions

MHLC Form B

This is a questionnaire designed to determine the way in which different people view certain important health-related issues. Each item is a belief statement with which you may agree or disagree. Beside each statement is a scale which ranges from strongly disagree (1) to strongly agree (6). For each item we would like you to circle the number that represents the extent to which you disagree or agree with the statement. The more strongly you agree with a statement, then the higher will be the number you circle. The more strongly you disagree with a statement then the lower will be the number you circle. Please make sure that you answer every item and that you circle only one number per item. This is a measure of you personal beliefs; obviously, there are no right or wrong answers.

Please answer these items carefully, but do not spend too much time on any one item. As much a you can, try to respond to each item independently. When making your choice, do not be influenced by your previous choices. It is important that you respond according to your actual beliefs and not according to how you feel you should believe or how you think we want you to believe.

| | | Strongly Disagree | Moderately Disagree | Slightly Disagree | Slightly Agree | Moderately Agree | Strongly Agree |
|---|---|---|---|---|---|---|---|
| 1. | If I become sick, I have the power to make myself well again. | 1 | 2 | 3 | 4 | 5 | 6 |
| 2. | Often I feel that no matter what I do, if I am going to get sick, I will get sick. | 1 | 2 | 3 | 4 | 5 | 6 |
| 3. | If I see an excellent doctor regularly, I am less likely to have health problems. | 1 | 2 | 3 | 4 | 5 | 6 |
| 4. | It seems that my health is greatly influenced by accidental happenings. | 1 | 2 | 3 | 4 | 5 | 6 |
| 5. | I can only maintain my health by consulting health professionals. | 1 | 2 | 3 | 4 | 5 | 6 |
| 6. | I am directly responsible for my health. | 1 | 2 | 3 | 4 | 5 | 6 |
| 7. | Other people play a big part in whether I stay healthy or become sick. | 1 | 2 | 3 | 4 | 5 | 6 |
| 8. | Whatever goes wrong with my health is my own fault. | 1 | 2 | 3 | 4 | 5 | 6 |
| 9. | When I am sick, I just have to let nature run its course. | 1 | 2 | 3 | 4 | 5 | 6 |
| 10. | Health professionals keep me healthy. | 1 | 2 | 3 | 4 | 5 | 6 |
| 11. | When I stay healthy, I'm just plain lucky. | 1 | 2 | 3 | 4 | 5 | 6 |
| 12. | My physical well-being depends on how well I take care of myself. | 1 | 2 | 3 | 4 | 5 | 6 |
| 13. | When I feel ill, I know it is because I have not been taking care of myself properly. | 1 | 2 | 3 | 4 | 5 | 6 |
| 14. | The type of care I receive from other people is what is responsible for how well I recover from an illness. | 1 | 2 | 3 | 4 | 5 | 6 |
| 15. | Even when I take care of myself, it's easy to get sick. | 1 | 2 | 3 | 4 | 5 | 6 |
| 16. | When I become ill, it's a matter of fate. | 1 | 2 | 3 | 4 | 5 | 6 |
| 17. | I can pretty much stay healthy by taking good care of myself. | 1 | 2 | 3 | 4 | 5 | 6 |
| 18. | Following doctor's orders to the letter is the best way for me to stay healthy. | 1 | 2 | 3 | 4 | 5 | 6 |

## Appendix 2 Item 13. Middlesex Health Questionnaire questions

M H Q

| | | | | |
|---|---|---|---|---|
| 1. | Do you often feel upset for no obvious reason? | Yes | No | |
| 2. | Do you have an unreasonable fear of being in enclosed spaces such as shops, lifts etc.? | Frequently | Occasionally | Never |
| 3. | Do people ever say you are too conscientious? | Yes | No | |
| 4. | Are you troubled by dizziness or shortness of breath? | Never | Often | Sometimes |
| 5. | Can you think as quickly as you used to? | Yes | No | |
| 6. | Are your opinions easily influenced? | Yes | No | |
| 7. | Have you felt as though you might faint? | Frequently | Occasionally | Never |
| 8. | Do you find yourself worrying about getting some incurable illness? | Never | Often | Sometimes |
| 9. | Do you think that 'cleanliness is next to godliness'? | Yes | No | |
| 10. | Do you often feel sick or have indigestion? | Yes | No | |
| 11. | Do you feel that life is too much effort? | At times | Often | Never |
| 12. | Have you, at any time in your life, enjoyed acting? | Yes | No | |
| 13. | Do you feel uneasy and restless? | Frequently | Occasionally | Never |
| 14. | Do you feel more relaxed indoors? | Definitely | Not particularly | Sometimes |
| 15. | Do you find that silly or unreasonable thoughts keep recurring in your mind? | Frequently | Sometimes | Never |
| 16. | Do you sometimes feel tingling or prickling sensations in your body, arms or legs? | Frequently | Rarely | Never |
| 17. | Do you regret much of your past behaviour? | Yes | No | |
| 18. | Are you normally an excessively emotional person? | Yes | No | |
| 19. | Do you sometimes feel really panicky? | Yes | No | |
| 20. | Do you feel uneasy travelling on buses or the underground even if they are not crowded? | Very | A little | Not at all |
| 21. | Are you happiest when you are working? | Yes | No | |
| 22. | Has your appetite got less recently? | Yes | No | |
| 23. | Do you wake unusually early in the morning? | Yes | No | |
| 24. | Do you enjoy being the centre of attention? | Yes | No | |
| 25. | Would you say you were a worrying person? | Very | Fairly | Not at all |
| 26. | Do you dislike going out alone? | Yes | No | |

| | | | | |
|---|---|---|---|---|
| 27. | Are you a perfectionist? | Yes | No | |
| 28. | Do you feel unduly tired and exhausted? | Never | Often | Sometimes |
| 29. | Do you experience long periods of sadness? | Never | Often | Sometimes |
| 30. | Do you find that you take advantage of circumstances for your own ends? | Never | Often | Sometimes |
| 31. | Do you often feel 'strung-up' inside? | Yes | No | |
| 32. | Do you worry unduly when relatives are late coming home? | Yes | No | |
| 33. | Do you have to check things you do to an unnecessary extent? | Yes | No | |
| 34. | Can you get off to sleep alright at the moment? | Yes | No | |
| 35. | Do you have to make a special effort to face up to a crisis or difficulty? | Very much so | Sometimes | Not more than anyone el: |
| 36. | Do you often spend a lot of money on clothes? | Yes | No | |
| 37. | Have you ever had the feeling you were 'going to pieces'? | Yes | No | |
| 38. | Are you scared of heights? | Very | Fairly | Not at all |
| 39. | Does it irritate you if your normal routine is disturbed? | Greatly | A little | Not at all |
| 40. | Can you often suffer from excessive sweating or fluttering of the heart? | Yes | No | |
| 41. | Do you find yourself needing to cry? | Frequently | Sometimes | Never |
| 42. | Do you enjoy dramatic situations? | Yes | No | |
| 43. | Do you have bad dreams which upset you when you wake up? | Frequently | Sometimes | Never |
| 44. | Do you feel panicky in crowds? | Always | Sometimes | Frequently Never |
| 45. | Do you find yourself worrying unreasonably about things that do not really matter? | Frequently | Sometimes | Never |
| 46. | Has your sexual interest altered? | Less | The same or greater | |
| 47. | Have you lost your ability to feel sympathy for other people? | Yes | No | |
| 48. | Do you sometimes find yourself posing or pretending? | Yes | No | |

# APPENDIX 3

# PREPARATORY STATISTICAL ANALYSIS

**Appendix 3 Table 1 Proportion of subjects calculated in results for cognitive tests .**

This Table shows the number and percentage of subjects for whom data was collected on each individual test.

First testing

| | CFS | Normal | Crohns/colitis |
|---|---|---|---|
| Logical Memory | 45 (100%) | 41 (100%) | 23 (100%) |
| Digit | 45 (100%) | 41 (100%) | 23 (100%) |
| Associate Learning | 43 (96%) | 41 (100%) | 23 (100%) |
| Word Fluency | 45 (100%) | 39 (95%) | 23 (100%) |
| WAIS Symbols | 44 (98%) | 41 (100%) | 23 (100%) |
| WAIS Blocks | 35 (78%) | 37 (90%) | 11 (48%) |
| Reaction Time | 44 (98%) | 39 (95%) | 23 (100%) |
| Threshhold | 38 (84%) | 40 (98%) | 21 (91%) |
| Visual Span | 45 (100%) | 41 (100%) | 22 (96%) |
| PASAT | 40 (89%) | 37 (98%) | 8 (35%) |
| Word Recall | 43 (96%) | 41 (100%) | 23 (100%) |
| Stroop Reading | 38 (84%) | 40 (98%) | 23 (100%) |
| REY Copy | 45 (100%) | 41 (100%) | 21 (91%) |
| REY Memory | 43 (96%) | 38 (93%) | 19 (83%) |
| CES-D | 45 (100%) | 41 (100%) | 22 (96%) |
| Anxiety - State | 45 (100%) | 41 (100%) | 23 (100%) |
| - Trait | 43 (96%) | 41 (100%) | 23 (100%) |
| Finger Tapping | 23 (51%) | 38 (93%) | 17 (74%) |
| Stroop Colours | 25 (56%) | 39 (95%) | 23 (100%) |
| Fatigue | 44 (98%) | 41 (100%) | 23 (100%) |
| Symptoms | 45 (100%) | 41 (100%) | 23 (100%) |

**Appendix 3 Table 1 Proportion of subjects calculated in results for cognitive tests: continued**

Second testing

| | CFS | Normal | Crohns/colitis | |
|---|---|---|---|---|
| Logical Memory | 37 (82%) | 23 (56%) | 16 (70%) | |
| Digit | 37 (82%) | 23 (56%) | 15 (65%) | |
| Associate Learning | 36 (80%) | 23 (56%) | 16 (70%) | |
| Word Fluency | 37 (82%) | 23 (56%) | 17 (74%) | |
| WAIS Symbols | 36 (80%) | 23 (56%) | 17 (74%) | |
| WAIS Blocks | 31 (69%) | 22 (54%) | 8 (35%) | |
| Reaction Time | 37 (82%) | 23 (56%) | 18 (78%) | |
| Threshhold | 37 (82%) | 23 (56%) | 16 (70%) | |
| Visual Span | 37 (82%) | 22 (54%) | 16 (70%) | |
| PASAT | 36 (80%) | 22 (54%) | 8 (35%) | |
| Word Recall | 37 (82%) | 24 (59%) | 17 (74%) | |
| Stroop Reading | 37 (82%) | 18 (44%) | 15 (65%) | |
| REY Copy | 37 (82%) | 22 (54%) | 16 (70%) | |
| REY Memory | 37 (82%) | 20 (49%) | 16 (70%) | |
| | | | | |
| CES-D | 37 (82%) | 21 (51%) | 17 (74%) | |
| Anxiety - State | 37 (82%) | 20 (49%) | 17 (74%) | |
| - Trait | 36 (80%) | 20 (49%) | 17 (74%) | |
| | | | | |
| Finger Tapping | 22 (49%) | 21 (51%) | 15 (65%) | |
| Stroop Colours | 35 (78%) | 21 (51%) | 17 (74%) | |
| | | | | |
| Fatigue | 37 (82%) | 20 (49%) | 17 (74%) | |
| Symptoms | 37 (82%) | 21 (51%) | 17 (74%) | |
| | | | | |
| Others | | | | |
| | | | | |
| NART | 42 (93%) | 36 (88%) | 22 (96%) | |
| | | | | |
| Psychiatric questionnaires | 41 (91%) | 30 (73%) | 19 (83%) | (*) |
| | | | | |
| Questionnaire general questions | 47 (104%) | 41 (100%) | 26 (113%) | (*) |
| | | | | |
| Being ill Questionnaire Variables (cf App. 9 Table 3b) | 46 (102%) | - | 25 (109%) | (*) |

(*) Note that questionnaire data was collected from two CFS patients and three Crohns/colitis patients who were excluded from the cognitive tests.

## Appendix 3 Table 2: Distributions

Note that some data were collected by questionnaire, so there are a few data-points missing. The figure given are percentages, with the absolute numbers of subjects given in brackets.

**Table 2A: Age distribution of subjects**

| Age | CFS (%) | Normal Controls (%) | Chronic Controls (%) |
|---|---|---|---|
| 16-20 | 7 ( 3) | 17 ( 7) | 4 ( 1) |
| 21-25 | 23 (10) | 27 (11) | 22 ( 6) |
| 26-30 | 16 ( 7) | 12 ( 5) | 7 ( 2) |
| 31-35 | 18 ( 8) | 12 ( 5) | 19 ( 5) |
| 36-40 | 7 ( 3) | 5 ( 2) | 22 ( 6) |
| 41-45 | 11 ( 5) | 7 ( 3) | 4 ( 1) |
| 46-50 | 7 ( 3) | 5 ( 2) | 11 ( 3) |
| 51-55 | 5 ( 2) | 7 ( 5) | 4 ( 1) |
| 56-60 | 7 ( 3) | 7 ( 5) | 7 ( 2) |
| | 100 (44) | 100 (41) | 100 (27) |
| | (n=44) | (n=41) | (n=27) |

**Table 2B: IQ distribution of subjects**

| NART | IQ | CFS (%) | Normal Controls (%) | Chronic Controls (%) |
|---|---|---|---|---|
| 0- 9 | 120+ | 21 ( 9) | 11 ( 4) | 14 ( 3) |
| 10-22 | 110-120 | 55 (23) | 50 (18) | 41 ( 9) |
| 23-34 | 100-110 | 21 ( 9) | 33 (12) | 36 ( 8) |
| 35-50 | 90-100 | 2 ( 1) | 6 ( 2) | 9 ( 2) |
| | | 100 (42) | 100 (36) | 100 (22) |
| | | (n=42) | (n=36) | (n=22) |

**Table 2C: Fatigue distribution of subjects**

| Fatigue | | CFS (%) | Normal Controls (%) | Chronic Controls (%) |
|---|---|---|---|---|
| (Exhausted) | 0 | 0 ( 0) | 2 ( 1) | 4 ( 1) |
| | 1 | 18 ( 8) | 0 ( 0) | 0 ( 0) |
| | 2 | 25 (11) | 0 ( 0) | 9 ( 2) |
| | 3 | 23 (10) | 12 ( 5) | 17 ( 4) |
| | 4 | 11 ( 5) | 7 ( 3) | 0 ( 0) |
| | 5 | 9 ( 4) | 17 ( 7) | 17 ( 4) |
| | 6 | 7 ( 3) | 7 ( 3) | 0 ( 0) |
| | 7 | 2 ( 1) | 2 ( 1) | 26 ( 6) |
| | 8 | 2 ( 1) | 34 (14) | 17 ( 4) |
| | 9 | 2 ( 1) | 17 ( 7) | 9 ( 2) |
| (Energetic) | 10 | 0 ( 0) | 0 ( 0) | 0 ( 0) |
| | | 100 (44) | 100 (41) | 100 (23) |
| | | (n=44) | (n=41) | (n=23) |

**Table 2D: Symptom distribution of subjects**

| Symptom points | CFS (%) | Normal Controls (%) | Chronic Controls (%) |
|---|---|---|---|
| 0 | 0 ( 0) | 12 ( 5) | 0 ( 0) |
| 1- 5 | 4 ( 2) | 46 (19) | 48 (11) |
| 6-10 | 2 ( 1) | 12 ( 5) | 30 ( 7) |
| 11-20 | 20 ( 9) | 17 ( 7) | 13 ( 3) |
| 21-30 | 18 ( 8) | 10 ( 4) | 9 ( 2) |
| 31-40 | 16 ( 7) | 0 ( 0) | 0 ( 0) |
| 41-50 | 7 ( 3) | 2 ( 1) | 0 ( 0) |
| 51-60 | 13 ( 6) | 0 ( 0) | 0 ( 0) |
| 61-70 | 16 ( 7) | 0 ( 0) | 0 ( 0) |
| 71-80 | 2 ( 1) | 0 ( 0) | 0 ( 0) |
| 81-90 | 0 ( 0) | 0 ( 0) | 0 ( 0) |
| 91-100 | 2 ( 1) | 0 ( 0) | 0 ( 0) |
| | 100 (45) | 100 (41) | 100 (23) |
| | (n=45) | (n=41) | (n=23) |

**Table 2E Depression distribution of subjects**

| CES-D | CFS (%) | Normal Controls (%) | Chronic Controls (%) |
|---|---|---|---|
| 0- 5 | 7 ( 3) | 46 (19) | 50 (11) |
| 6-10 | 11 ( 5) | 34 (14) | 27 ( 6) |
| 11-15 | 22 (10) | 5 ( 2) | 18 ( 4) |
| 16-20 | 13 ( 6) | 10 ( 4) | 5 ( 1) |
| 21-25 | 27 (12) | 0 ( 0) | 0 ( 0) |
| 26-30 | 11 ( 5) | 2 ( 1) | 0 ( 0) |
| 31-35 | 7 ( 3) | 0 ( 0) | 0 ( 0) |
| 36-40 | 2 ( 1) | 0 ( 0) | 0 ( 0) |
| 41-45 | 0 ( 0) | 2 ( 1) | 0 ( 0) |
| | 100 (45) | 100 (41) | 100 (22) |
| | (n=45) | (n=41) | (n=22) |

**Table 2F Proportion of subjects having prior serious illness**

| CFS (%) | Normal Controls (%) | Chronic Controls (%) |
|---|---|---|
| 34 (16) | 5 (2) | 20 (5) |
| (n=47) | (n=38) | (n=25) |

**Table 2G Proportion of subjects having contact with trigger illness**

| CFS (%) | Normal Controls (%) | Chronic Controls (%) |
|---|---|---|
| 62 (29) | 28 (11) | 35 ( 9) |
| (n=47) | (n=39) | (n=26) |

**Table 2H Distribution of length of illness of subjects**

| Length (years) | CFS (%) | Chronic Controls (%) |
|---|---|---|
| 0- 1 | 7 ( 3) | 0 ( 0) |
| 1- 2 | 23 (10) | 17 ( 3) |
| 2- 3 | 23 (10) | 17 ( 3) |
| 3- 4 | 11 ( 5) | 11 ( 2) |
| 4- 5 | 20 ( 9) | 11 ( 2) |
| 5-10 | 11 ( 5) | 28 ( 5) |
| 10-15 | 5 ( 2) | 11 ( 2) |
| 15-21 | 2 ( 1) | 6 ( 1) |
| | 100 (45) | 100 (18) |
| | (n=45) | (n=18) |

**Table 2Ia Employment distribution of subjects**

| | CFS (%) | Normal Controls (%) | Chronic Controls (%) |
|---|---|---|---|
| Not working | 45 (20) | 5 ( 2) | 23 ( 6) |
| Working | 43 (19) | 82 (31) | 73 (19) |
| Students | 11 ( 5) | 13 ( 5) | 4 ( 1) |
| | (n=44) | (n=38) | (n=26) |

Significant on a chi-squared test, $p<0.001$

**Table 2Ib Breakdown of CFS employment**
(absolute numbers)

| | Not working | Working/ students | |
|---|---|---|---|
| Stopped work due to illness | 5 | 6 | Off sick |
| Lost work due to illness | 2 | 10<br>3 | Working<br>Part-time |
| Retired due to illness | 3 | | (2 reduced) |
| Redundancy | 1 | 19 | |
| Others: | | 5 | students |
| Not working but impatient to return | 7 | | (4 absent) |
| Not working other | 2 | | |
| | 20 | 24 | |

## Appendix 3 Table 3: Reasons for non-inclusion of potential subjects

Consultants decided not to send people to the study for reasons other than the exclusion criteria, for example:

1. The consultant judged that it was a particularly unsuitable time to ask the patients to join in the study because, for example, the patient was in a bad mood or the patient was particularly sick or the consultant was discussing an imminent operation.
2. The case was complicated by other medical problems or diagnosis was uncertain.
3. The patient would not have understood what they were being asked to do.

The experimenter rejected subjects for the study for the following reasons.

1. They were found to meet exclusion criteria before or during the study.
2. They had complicating aspects to their medical history, such as other medical conditions.
3. They were unable or unwilling to complete the study.

The details of how this worked out in practice are as follows.

(i) CFS group

Consultants rejections

Subjects who were referred to the experimenter as willing and suitable to take part but were not included in the study are as follows:-

1 under age
1 had fractured skull at 4
1 was excluded because of having anorexia and a history of abuse
1 too ill to attend
7 did not attend
3 cancelled.

2nd Testing

The reasons for not attending at second testing were not always known, but those known were as follows:-

2 moved away
1 was afraid the tests would make the illness worse - illness perceived worse by patient
1 in hospital
3 found it inconvenient to be retested as they had returned to work.

(ii) Normal group

The experimenter did not include:-

1 subject who had low IQ (difficulty measuring on NART) and emotional difficulties: she did not understand what was being asked of her
1 subject with very low IQ could not be matched with CFS patients
1 subject had a peculiar and inappropriately familiar response to experimenter: experimenter suspected psychiatric condition
1 excluded due to depression criteria
1 cancelled
24 did not attend.

(iii) Crohns/colitis group

Consultants rejections

8-12 were deemed unsuitable due to current depression, psychiatric history or upset in consultants appointment
2 were above the age limit
2 suffered head injury.

Subjects who were referred to the experimenter as willing and suitable to take part but then excluded by the experimenter at first testing were as follows:-

1 was rejected due to epilepsy
1 was unwilling
3 had suffered serious depressive illness
1 subject's spouse had CFS and the subject was also depressed
1 had suffered fractured skull at 5 years old
1 was above the age limit.
2 cancelled
3 did not attend

Subjects who were referred to the experimenter as willing and suitable to take part but then excluded by the experimenter at second testing were as follows:-

2 were too ill to carry out a second testing
1 returned to work
1 changed work shifts
2 had been prescribed antidepressants since first testing.

## Appendix 3 Table 4: Subjects' drug taking

The following table shows the drugs recorded as being taken by subjects during the study; the number of patients taking the drug is in brackets.

CFS patients
Anti-inflamatories
Naprosyn (1)
Brufen (Ibuprofen) (1)

Pain Killers
Co-proxamol (2)
Paracetamol (1)

Asthma
Ventolin(2)
Another (Thalbutomol) (1)

Crohns/colitis
For the bowel disorder
Salazopryn (Sulphasalazine) (8)
Prednisolone(Sodium Phosphate)(2)
Pentasa (3)
Asacol (1)
Colifoam (1)

Anti-inflamatory
Brufen (2)

Normal Controls
Anti-inflamatory
Brufen (1)
Naprosyn (1)
Asthma
Ventolin (1)
Moduretic (1)

Contraceptive Pill (4)

For Dizziness and/or sickness
Stemetil (1)
Stugeron (2)

Anti-acid Zantac (1)
Hormone-replacement-therapy (2)
Contraceptive pill (1)

Creams
Hydrocortisone (1)
Nystatin (1)

Painkillers
Codeine phosphate (1)
Iron suplements (2)

# APPENDIX 4

# VERSIONS

## Appendix 4 Table 1 Associate Learning: Statistics on Versions

The number of subjects on which each version of the Associate Learning test was used was as follows:

| | | <------ GROUP ------> | | |
|---|---|---|---|---|
| | Version | CFS | Normal | Chronic |
| 1st testing | 1 | 24 | 23 | 13 |
| | 2 | 19 | 18 | 10 |
| 2nd testing | 1 | 13 | 9 | 8 |
| | 2 | 23 | 14 | 8 |

In order to find out if the distribution of test-versions amongst subject-groups was even, a chi-square test was carried out on the distribution of versions amongst subject-groups for each testing. The results of the Chi-square statistic were 0.003 and 0.90 for the two tables respectively (with 2 d.f.), neither were significant at the 5% level. Therefore the null hypothesis, that there was not an uneven distribution of test-versions amongst subject-groups, was not rejected.

The chi-square test shows that the test-versions are not unevenly distributed, therefore it needs to be shown that the resulting scores are not significantly different between the test-versions. An ANOVA of the scores on first-testing taken categorising subjects by Group and Version showed the effect of the Version significant at 0.174 (an F-statistic of 22.72, with 1,101 d.f.). A similar ANOVA on the second-testing scores showed the effect of the Version significant at 0.089 (an F-statistic of 40.15, with 1,69 d.f.)
The null hypothesis that the test-versions have the same mean score is not rejected.

The overall mean scores for the Associate Learning test, including both first and second testing, were as follows:

| Version | Mean score |
|---|---|
| 1 | 14.47 |
| 2 | 14.43 |

## Appendix 4 Table_2 Logical Memory: Statistics on Versions

The number of subjects on which each version of the Logical Memory test was used was as follows:

| | | <------ GROUP ------> | | |
|---|---|---|---|---|
| | Version | CFS | Normal | Chronic |
| 1st testing | 1 | 16 | 19 | 7 |
| | 2 | 23 | 18 | 12 |
| | 3 | 6 | 4 | 4 |
| 2nd testing | 1 | 16 | 6 | 7 |
| | 2 | 20 | 9 | 9 |
| | 3 | 1 | 8 | 0 |

The scores derived from the versions were different: for the first testing, an ANOVA of the scores taken categorising subjects by Group and Version showed the effect of the Version significant at 0.007 (an F-statistic of 7.537, with 1,89 d.f.).

Thus, the raw scores cannot be used as they are, but must be weighted to remove the effect of the Version. (Alternatively, the raw scores and version numbers could both be put into the main ANOVA tests, but there is insufficient data to gain significant results from this.) Because the test-versions are not distributed perfectly evenly between the Groups, weighting scores by the mean Version-score would give inaccurate results, being affected by the number of each Group given that version. Therefore, the raw scores are converted in Z-scores depending on the Version, but the calculation is adjusted to take into account the numbers of each Group taking each Version (see Table 5).

A Chi-square test on the distribution of test-versions amongst subject-groups at the first testing gave a Chi-square statistic (with 4 d.f.) of 2.13, not significant at the 5% level, showing that this distribution was not uneven.

## Appendix 4 Table 3 Word Fluency: Statistics on Versions

The number of subjects on which each version of the Word Fluency test was used was as follows:

| | | <------ GROUP ------> | | |
|---|---|---|---|---|
| | Version | CFS | Normal | Chronic |
| 1st testing | 1 | 20 | 16 | 13 |
| | 2 | 17 | 16 | 7 |
| | 3 | 8 | 7 | 3 |
| 2nd testing | 1 | 13 | 8 | 8 |
| | 2 | 22 | 13 | 8 |
| | 3 | 2 | 2 | 1 |

In order to show that there was an even distribution of test-versions amongst subject-groups, a Chi-square test was carried out on the distribution of versions amongst subject-groups for each testing. The values of the Chi-square statistic found were 1.48 and 1.08 for the two tables respectively (with 4 d.f.), neither were significant at the 5% level. Therefore the null hypothesis, that there was not an uneven distribution of test-versions amongst subject-groups, was not rejected.

The scores derived from the versions on the Hardest Letter test were different: for the first testing, an ANOVA of the scores taken categorising subjects by Group and Version showed the effect of the Version significant for the Hardest Letter test-scores at 0.001 (an F-statistic of 21.42, with 2,98 d.f.) and for the Categories test-scores at 0.079 (an F-statistic of 2.61, with 2,98 d.f.)

Therefore, the raw scores cannot be used as they are, but must be weighted to remove the effect of the Version. (Alternatively, the raw scores and version numbers could both be put into the main ANOVA tests, but there is insufficient data to gain significant results from this.) Because the test-versions are not distributed perfectly evenly between the Groups, weighting scores by the mean Version-score would give inaccurate results, being affected by the number of each Group given that version. Therefore, the raw scores are converted in Z-scores depending on the Version, but the calculation is adjusted to take into account the numbers of each Group taking each Version (see Table 5). For consistency, both Categories and Hardest Letter scores were so weighted.

## Appendix 4 Table 5 Weighting Scores

As discussed in Tables 1-4, some of the raw test-results have to be weighted due to different test-versions being used. Although test versions are not unevently distributed they are not distributed perfectly evenly between the Groups. Therefore weighting scores by the mean Version-score could give slightly inaccurate results, being affected by the number of each Group given that version. Therefore, the raw scores are converted in Z-scores depending on the Version, but the calculation is adjusted to take into account the numbers of each Group taking each Version. This Table gives the details of that calculation.

Z-scores are found by subtracting the mean and then dividing by the standard deviation.

The mean is found by first calculating the mean score for *each* subject type for *each* version; then the mean that *would* have been obtained for Version 1 had there been a perfect distribution amongst the subject-types is as follows:

(Mean for CFS for version 1) x (proportion subjects that are CFS)
+ (Mean for Normals for v. 1) x (proportion subjects that are Normals)
+ (Mean for Chronics for v. 1) x (proportion subjects that are Chronics)

The standard deviation is found by taking the square-root of the variance that *would* have been obtained had there been a perfect distribution amongst the subject-types; the variance for Version 1 is as follows:

(Variance for CFS for version 1) x (proportion subjects that are CFS)
+ (Variance for Normals for v. 1) x (proportion subjects that are Normals)
+ (Variance for Chronics for v. 1) x (proportion subjects that are Chronics)

Given this mean and standard deviation, the scores on Version 1 can be converted to a Z-score. A similar calculation can be carried out for Version 2 and, for tests with three Versions, version 3.

# APPENDIX 5

# TESTS FOR NORMALITY

## Appendix 5 Tests for Normality

The statistical analysis in this thesis uses a number of parametric tests such as ANOVA. Such tests assume that the variables are Normally distributed within the groups, and furthermore that the variance is constant between the groups. This Appendix looks at the data, to consider whether there is significant non-Normality, whether data needs to be transformed, and possible "ceiling" effects.

### Normality

Normality is studied by visually inspecting the distribution, and quantitatively by looking at the Skew and Kurtosis. If either of these latter is significantly different from zero, then Normality cannot be assumed. Typically (see e.g. Tabachnick and Fidell (1989)), a significance level of 0.01 is used, so a null hypothesis of a parameter being zero is rejected if it is more than 2.5 standard deviations from the mean. The following Tables 1-3 show, for the three groups (as raw output from SPSS), the values of Skew and Kurtosis (and their Standard Errors) for the all of the variables in the analysis.

All of the variables shown in the tables satisfy the normality tests except the following:

(i) Word Fluency results that are *uncorrected*: these can be ignored, as only the corrected versions are used, and indeed this supports the need for correction (as described in Appendix 3).

(ii) Depression (CES-D). This is because CES-D is lower-bounded by zero (and only 5% of the sample actually achieved a value of zero). Taking Log(CES-D) would therefore avoid this problem. However, Log of zero is not defined, so we add 1 to the depression score before taking the Log. One CFS outlier is removed as being beyond 2.5 standard deviations from the mean. The remainder can be seen below to satisfy the Normal criteria. This variable will be used in place of CES-D in the analysis.

(iii) Visual Span; however LOG (Visual Span) satisfies the Normal criteria, as shown in the Tables. This variable will be used in place of the raw Visual Span score.

(iv) Rey Copy has a ceiling and is significantly non-Normal. The non-Normality in this variable should be noted, and any results gained considered in the light of this. In fact, this ceiling and the discreteness of the results meant that no significant results were gained from this variable.

(v) State Anxiety; again, LOG (State Anxiety) is much nearer normal, although there is still a little too much Kurtosis in the CFS patients.

(vi) Both Stroop Reading and Colours. Again, LOG of both of these is much nearer Normal. In the case of CFS patients, there is one Outlier, and Table 2 shows that when this outlier is removed, the distribution is closer to Normality. LOG variables are thus used in the data, and the outlier ignored for these tests (second-testing of Stroop also removed for this outlier, as the subject will have practised).

(vii) Both of the Symptoms variables are significantly non-Normal; again these are bounded by zero. LOG of the variables (again with one added to the scores to avoid taking the Log of zero) is much closer to Normal, and these variables will be used in the analysis. However, it should be noted that the CFS Symptoms figures are now negatively skewed, and this will be considered further in the analysis.

Homogeneity of variance

SPSS provides the Levene test to check for homogeneity of variance, which is assumed by ANOVA. Table 4 shows the values of the Levene test taken by the variables in the First testing shown in Tables 1-3 when the data is divided into the three subject types.

Some of these variables are no longer relevant, for the reasons discussed under "Normality" above: relevant variables are marked with a (*).

Of the relevant variables, four show a significant difference in variance:
Log (CES-D), Reaction Time Decision and Movement Time, and Finger Tapping
On these four tests, CFS patients are significantly worse *and more variable*, and this will need to be considered in the analysis.

**Appendix 5 Table 1. Summary statistics for CFS subjects**

| Variable | Kurtosis | Stand.Error of Kurtotis | Skewness | Stand.Error of Skewness | N |
|---|---|---|---|---|---|
| Logical memory(uncorrected | .25 | .69 | .60 | .35 | 45 |
| Logical memory (corrected) | .81 | .69 | .72 | .35 | 45 |
| Associate learning | -.36 | .71 | -.13 | .36 | 43 |
| Word recognition: | | | | | |
| Correct | -.35 | .73 | -.35 | .37 | 40 |
| Correct - Errors | -.32 | .73 | -.43 | .37 | 40 |
| Digit forward + digit back | -.92 | .69 | -.15 | .35 | 45 |
| Rey memory (uncorrected) | -.55 | .71 | .10 | .36 | 43 |
| Rey memory (corrected) | -.37 | .71 | .21 | .36 | 43 |
| Rey Copy | .48 | .69 | -1.25 | .35 | 45 |
| Threshold task (score) | -1.00 | .75 | .24 | .38 | 38 |
| Visual span | 3.88 | .69 | 1.08 | .35 | 45 |
| WAIS blocks (raw score) | -.32 | .78 | -.59 | .40 | 35 |
| Reaction time (milliseconds) | | | | | |
| Decision time | .01 | .70 | .58 | .36 | 44 |
| Movement time | -.92 | .69 | .44 | .35 | 45 |
| Finger Tapping (per minute) | -.86 | .90 | .21 | .46 | 25 |
| Language word fluency (per minute) | | | | | |
| Hard letter (uncorrected) | 2.80 | .69 | 1.35 | .35 | 45 |
| Hard letter (corrected) | -.43 | .69 | -.04 | .35 | 45 |
| Categories (uncorrected) | .66 | .69 | .75 | .35 | 45 |
| Categories (corrected) | .47 | .69 | .66 | .35 | 45 |
| Stroop Reading | .62 | .74 | .85 | .38 | 39 |
| Stroop Colours | 7.80 | .92 | 2.34 | .47 | 24 |
| PASAT (out of 60) | .22 | .73 | -.52 | .37 | 40 |
| WAIS Digit Symbol (raw) | -.24 | .70 | .25 | .36 | 44 |
| | | | | | |
| Mood: | | | | | |
| CES-D | -.39 | .69 | .04 | .35 | 45 |
| Anxiety: state | 2.79 | .69 | .94 | .35 | 45 |
| Anxiety: trait | .01 | .71 | .25 | .36 | 43 |
| Symptoms: that week | -.36 | .69 | .44 | .35 | 45 |
| now | 1.82 | .69 | 1.26 | .35 | 45 |
| Fatigue | .87 | .70 | 1.08 | .36 | 44 |
| | | | | | |
| Log-variables | | | | | |
| Log (CES-D) | .52 | .70 | -.86 | .36 | 44 |
| Log(Visual span) | .78 | .69 | -.40 | .35 | 45 |
| Log(Anxiety: state) | 2.53 | .69 | -.29 | .35 | 45 |
| Log(Stroop Colours) | 3.03 | .92 | 1.25 | .47 | 24 |
| Log(Stroop Reading) | -.17 | .74 | .28 | .38 | 39 |
| Log(Symptoms that week) | 1.16 | .69 | -1.07 | .35 | 45 |
| Log(Symptoms now) | .49 | .69 | -.97 | .35 | 45 |
| | | | | | |
| with single outlier removed: | | | | | |
| Log(Stroop Colours) | -.48 | .93 | .09 | .48 | 23 |
| Log(Stroop Reading) | -.10 | .75 | .34 | .38 | 38 |

**Appendix 5 Table 2. Summary statistics for Normal subjects**

| Variable | Kurt-osis | Stand.Error of Kurtotis | Skew-ness | Stand.Error of Skewness | N |
|---|---|---|---|---|---|
| Logical memory(uncorrected | -1.07 | .72 | -.01 | .37 | 41 |
| Logical memory (corrected) | -.53 | .72 | .02 | .37 | 41 |
| Associate learning | -.25 | .72 | -.54 | .37 | 41 |
| Word recognition: | | | | | |
| Correct | .13 | .74 | .27 | .38 | 39 |
| Correct - Errors | -.53 | .74 | -.59 | .38 | 39 |
| Digit forward + digit back | -.50 | .72 | -.32 | .37 | 41 |
| Rey memory (uncorrected) | -.03 | .75 | -.73 | .38 | 38 |
| Rey memory (corrected) | .14 | .75 | -.47 | .38 | 38 |
| Rey Copy | 3.21 | .72 | -1.69 | .37 | 41 |
| Threshold task (score) | 1.19 | .73 | -.32 | .37 | 40 |
| Visual span | .99 | .72 | .81 | .37 | 41 |
| WAIS blocks (raw score) | -.96 | .76 | -.27 | .39 | 37 |
| Reaction time (milliseconds) | | | | | |
| Decision time | -.17 | .74 | .16 | .38 | 39 |
| Movement time | -.35 | .73 | -.16 | .37 | 40 |
| Finger Tapping (per minute) | -.55 | .75 | .15 | .38 | 38 |
| Language word fluency (per minute) | | | | | |
| Hard letter (uncorrected) | .96 | .74 | 1.11 | .38 | 39 |
| Hard letter (corrected) | -.43 | .74 | .52 | .38 | 39 |
| Categories (uncorrected) | .82 | .74 | -.87 | .38 | 39 |
| Categories (corrected) | .63 | .74 | -.75 | .38 | 39 |
| Stroop Reading | .36 | .73 | .98 | .37 | 40 |
| Stroop Colours | 1.87 | .74 | 1.10 | .38 | 39 |
| PASAT (out of 60) | -1.32 | .76 | .21 | .39 | 37 |
| WAIS Digit Symbol (raw) | .16 | .72 | .57 | .37 | 41 |
| | | | | | |
| Mood: | | | | | |
| CES-D | 6.78 | .72 | 2.25 | .37 | 41 |
| Anxiety: state | 3.95 | .72 | 1.50 | .37 | 41 |
| Anxiety: trait | .61 | .72 | .75 | .37 | 41 |
| Symptoms: that week | 5.54 | .72 | 2.06 | .37 | 41 |
| now | 4.64 | .72 | 2.15 | .37 | 41 |
| Fatigue | -.32 | .72 | -.71 | .37 | 41 |
| | | | | | |
| Log-variables | | | | | |
| Log (CES-D) | -.16 | .72 | -.37 | .37 | 41 |
| Log(Visual span) | .08 | .72 | -.26 | .37 | 41 |
| Log(Anxiety: state) | .58 | .72 | .50 | .37 | 41 |
| Log(Stroop Colours) | 1.60 | .74 | .35 | .38 | 39 |
| Log(Stroop Reading) | -.21 | .73 | .63 | .37 | 40 |
| Log(Symptoms that week) | -.29 | .72 | .21 | .37 | 41 |
| Log(Symptoms now) | -.57 | .72 | .72 | .37 | 41 |

**Appendix 5 Table 3. Summary statistics for Chronic subjects**

| Variable | Kurtosis | Stand.Error of Kurtotis | Skewness | Stand.Error of Skewness | N |
|---|---|---|---|---|---|
| Logical memory(uncorrected | -.37 | .93 | .44 | .48 | 23 |
| Logical memory (corrected) | -.76 | .93 | .42 | .48 | 23 |
| Associate learning | -1.04 | .93 | -.38 | .48 | 23 |
| Word recognition: | | | | | |
| Correct | .34 | .95 | -.65 | .49 | 22 |
| Correct - Errors | -.60 | .97 | -.09 | .50 | 21 |
| Digit forward + digit back | -.87 | .93 | -.20 | .48 | 23 |
| Rey memory (uncorrected) | .12 | 1.01 | -.59 | .52 | 19 |
| Rey memory (corrected) | .40 | 1.01 | -.89 | .52 | 19 |
| Rey Copy | 9.94 | .97 | -3.07 | .50 | 21 |
| Threshold task (score) | 2.70 | .97 | 1.29 | .50 | 21 |
| Visual span | -.32 | .95 | .83 | .49 | 22 |
| WAIS blocks (raw score) | 2.95 | 1.28 | 1.64 | .66 | 11 |
| Reaction time (milliseconds) | | | | | |
| Decision time | 2.25 | .93 | -.34 | .48 | 23 |
| Movement time | -.40 | .93 | .31 | .48 | 23 |
| Finger Tapping (per minute) | 2.33 | 1.06 | -.62 | .55 | 17 |
| Language word fluency (per minute) | | | | | |
| Hard letter (uncorrected) | -.24 | .93 | .89 | .48 | 23 |
| Hard letter (corrected) | -1.12 | .93 | .17 | .48 | 23 |
| Categories (uncorrected) | 1.25 | .93 | -.73 | .48 | 23 |
| Categories (corrected) | 1.61 | .93 | .06 | .48 | 23 |
| Stroop Reading | .24 | .93 | .83 | .48 | 23 |
| Stroop Colours | 2.05 | .93 | .90 | .48 | 23 |
| PASAT (out of 60) | -1.53 | 1.48 | -.65 | .75 | 8 |
| WAIS Digit Symbol (raw) | 1.75 | .93 | -.38 | .48 | 23 |
| | | | | | |
| Mood: | | | | | |
| CES-D | -.66 | .95 | .53 | .49 | 22 |
| Anxiety: state | -.27 | .93 | -.30 | .48 | 23 |
| Anxiety: trait | -.61 | .93 | .02 | .48 | 23 |
| Symptoms: that week | 4.71 | .93 | 2.15 | .48 | 23 |
| now | 4.95 | .93 | 2.24 | .48 | 23 |
| Fatigue | -.79 | .93 | -.52 | .48 | 23 |
| | | | | | |
| Log-variables | | | | | |
| Log (CES-D) | -.70 | .95 | -.59 | .49 | 22 |
| Log(Visual span) | -.62 | .95 | .34 | .49 | 22 |
| Log(Anxiety: state) | .44 | .93 | -.85 | .48 | 23 |
| Log(Stroop Colours) | .66 | .93 | .23 | .48 | 23 |
| Log(Stroop Reading) | -.18 | .93 | .52 | .48 | 23 |
| Log(Symptoms that week) | .22 | .93 | .21 | .48 | 23 |
| Log(Symptoms now) | .08 | .93 | 1.26 | .48 | 23 |

**Appendix 5 Table 4. Levene's Test of homogeneity of variance**

| | | | df1 | df2 | Significance |
|---|---|---|---|---|---|
| Logical memory(uncorrected | (*) | .4427 | 2 | 106 | .6435 |
| Logical memory (corrected) | (*) | .4070 | 2 | 106 | .6667 |
| Associate learning | (*) | .5200 | 2 | 104 | .5960 |
| Word recognition: | | | | | |
| Correct | (*) | 1.3212 | 2 | 98 | .2715 |
| Correct - Errors | (*) | 3.5323 | 2 | 97 | .0331 |
| Digit forward + digit back | (*) | .0086 | 2 | 106 | .9915 |
| Rey memory (uncorrected) | (*) | 2.1033 | 2 | 97 | .1276 |
| Rey memory (corrected) | (*) | 1.8419 | 2 | 97 | .1640 |
| Rey Copy | | 5.2302 | 2 | 104 | .0068 |
| Threshold task (score) | (*) | 2.0200 | 2 | 96 | .1382 |
| Visual span | | .3475 | 2 | 105 | .7072 |
| WAIS blocks (raw score) | (*) | 1.0393 | 2 | 80 | .3584 |
| Reaction time (milliseconds) | | | | | |
| Decision time | (*) | 18.5636 | 2 | 103 | .0000 |
| Movement time | (*) | 14.8858 | 2 | 105 | .0000 |
| Finger Tapping (per minute) | (*) | 9.9008 | 2 | 77 | .0001 |
| Language word fluency (per minute) | | | | | |
| Hard letter (uncorrected) | | .8018 | 2 | 104 | .4513 |
| Hard letter (uncorrected) | (*) | .1601 | 2 | 104 | .8522 |
| Categories (uncorrected) | | 1.0709 | 2 | 104 | .3464 |
| Categories (corrected) | (*) | .8342 | 2 | 104 | .4371 |
| Stroop Reading | | 3.6183 | 2 | 99 | .0304 |
| Stroop Colours | | 1.8863 | 2 | 83 | .1581 |
| PASAT (out of 60) | (*) | .3968 | 2 | 82 | .6737 |
| WAIS Digit Symbol (raw) | (*) | .6883 | 2 | 105 | .5047 |
| | | | | | |
| Mood: | | | | | |
| CES-D | | 2.3482 | 2 | 105 | .1005 |
| Anxiety: state | | .0952 | 2 | 106 | .9093 |
| Anxiety: trait | (*) | .3202 | 2 | 104 | .7267 |
| Symptoms: that week | | 26.6804 | 2 | 106 | .0000 |
| now | | 21.2466 | 2 | 106 | .0000 |
| Fatigue | (*) | 3.1220 | 2 | 105 | .0482 |
| | | | | | |
| Log-variables | | | | | |
| Log (CES-D) | (*) | 6.1225 | 2 | 98 | .0031 |
| Log(Visual span) | (*) | .8494 | 2 | 105 | .4306 |
| Log(Anxiety: state) | (*) | 1.2146 | 2 | 106 | .3009 |
| Log(Stroop Colours) | (*) | .8580 | 2 | 83 | .4277 |
| Log(Stroop Reading) | (*) | 1.5932 | 2 | 99 | .2084 |
| Log(Symptoms that week) | (*) | .5259 | 2 | 101 | .5926 |
| Log(Symptoms now) | (*) | .1491 | 2 | 69 | .8617 |
| | | | | | |
| with single (CFS) outlier removed: | | | | | |
| Log(Stroop Colours) | (*) | .1680 | 2 | 82 | .8456 |
| Log(Stroop Reading) | (*) | 1.4789 | 2 | 98 | .2329 |

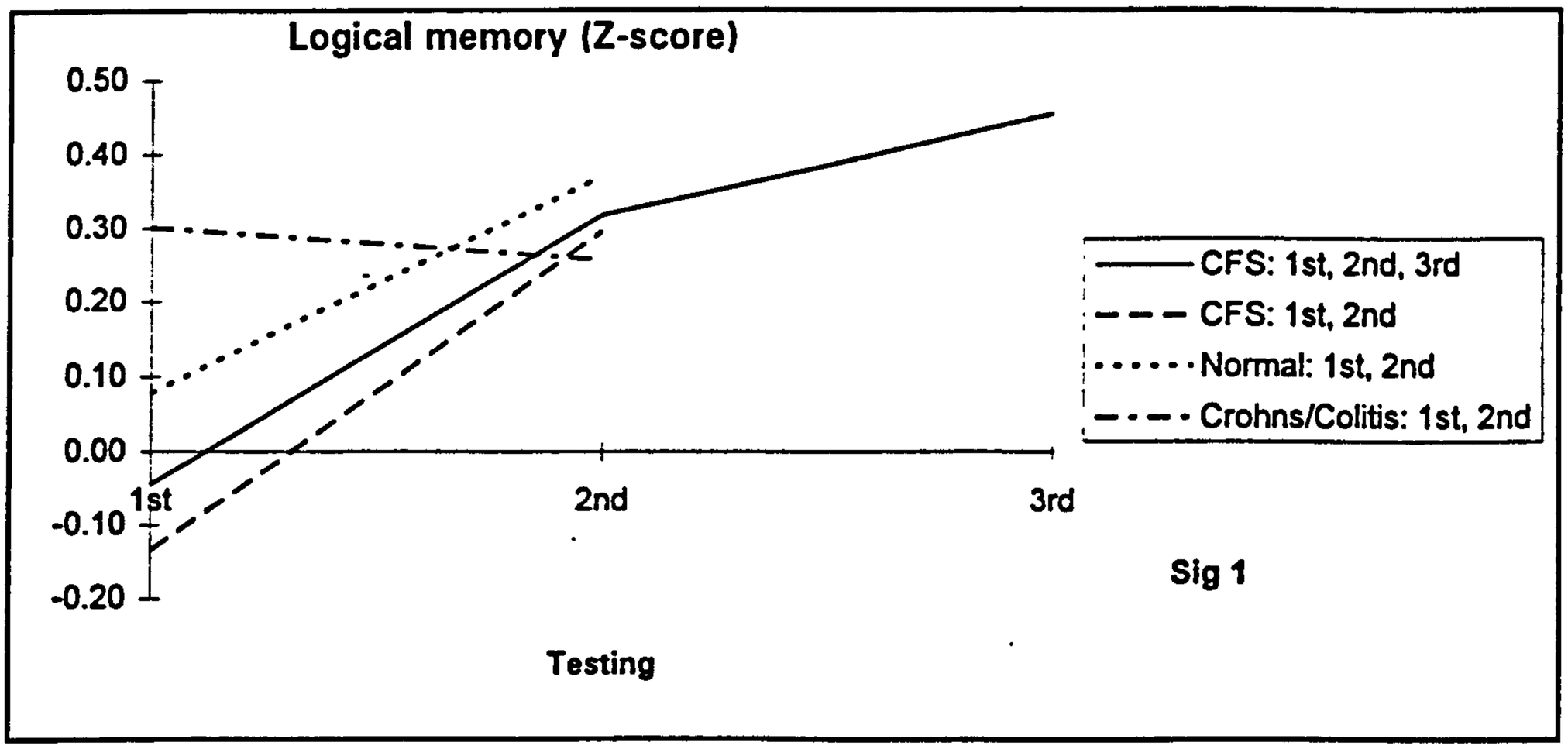
# APPENDIX 6

# MAIN RESULTS: GRAPHS

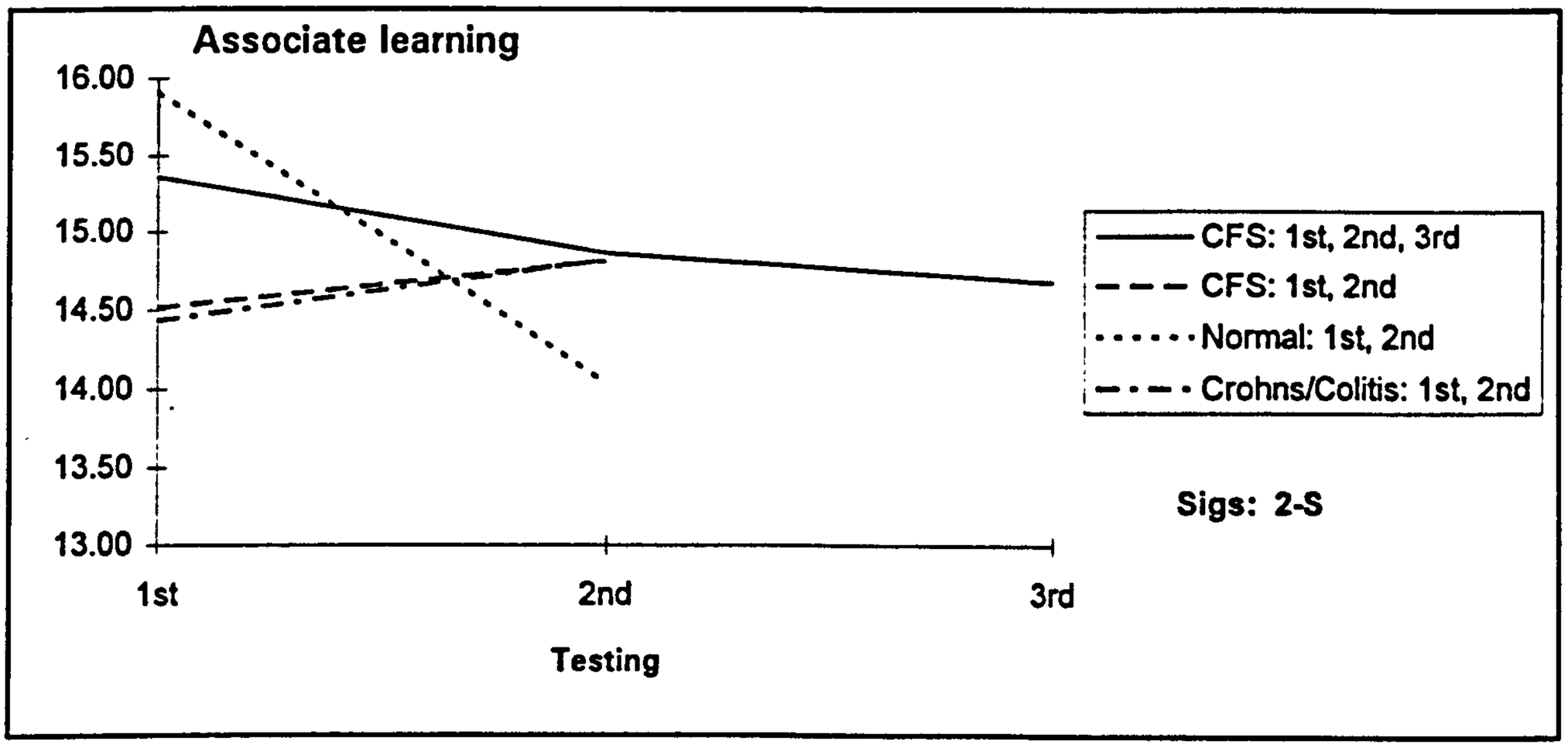
**Results of tests for subjects that carried out both 1st and 2nd testing**
**(Shown In Graphs)**

| Group: | CFS: 1st, 2nd | | | Normal: 1st, 2nd | | | Crohns/Colitis: 1st, 2nd | | | CFS patients for 1st, 2nd and 3rd testing | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Testing: | N= | 1st | 2nd | N= | 1st | 2nd | N= | 1st | 2nd | N= | 1st | 2nd | 3rd |
| *Memory Tasks* | | | | | | | | | | | | | |
| *(i) Language* | | | | | | | | | | | | | |
| Logical memory (Z-score) | 37 | -0.13 | 0.30 | 23 | 0.08 | 0.37 | 16 | 0.30 | 0.26 | 17 | -0.04 | 0.32 | 0.46 |
| Associate learning | 34 | 14.51 | 14.81 | 23 | 15.91 | 14.04 | 16 | 14.44 | 14.81 | 18 | 15.36 | 14.86 | 14.67 |
| Word recognition: Correct | 35 | 8.51 | 9.77 | 22 | 9.77 | 9.68 | 15 | 9.07 | 9.00 | 18 | 8.22 | 9.72 | 8.50 |
| Word recognition: Correct - Errors | 36 | 7.28 | 7.78 | 24 | 8.83 | 8.00 | 17 | 8.41 | 7.88 | 19 | 6.79 | 7.63 | 7.21 |
| *(iii) Other* | | | | | | | | | | | | | |
| Digit forward + digit back | 37 | 11.89 | 12.30 | 23 | 11.87 | 12.43 | 15 | 12.20 | 11.73 | 19 | 12.26 | 12.58 | 12.84 |
| Rey memory (Z-score) | 36 | -0.16 | 0.23 | 19 | 0.18 | 0.52 | 13 | -0.38 | -0.31 | 18 | 0.08 | 0.45 | 0.56 |
| Rey copy | 37 | 34.97 | 35.03 | 22 | 35.45 | 34.77 | 15 | 35.13 | 35.00 | 19 | 35.11 | 35.16 | 35.21 |
| Log(Visual span) | 37 | 1.09 | 1.05 | 22 | 1.00 | 1.04 | 15 | 1.06 | 1.03 | 19 | 1.08 | 1.07 | 1.07 |
| *Tasks requiring speed* | | | | | | | | | | | | | |
| *(i) Language* | | | | | | | | | | | | | |
| Stroop: Log(Reading) | 32 | 1.58 | 1.57 | 23 | 1.51 | 1.51 | 17 | 1.48 | 1.51 | 16 | 1.59 | 1.56 | 1.49 |
| Stroop: Log(Colours) | 18 | 1.90 | 1.87 | 22 | 1.86 | 1.88 | 17 | 1.83 | 1.83 | 6 | 1.91 | 1.89 | 1.66 |
| Word fluency (per min.) | | | | | | | | | | | | | |
| Hard letter (Z-score) | 33 | -0.01 | 0.31 | 21 | 0.33 | 0.48 | 17 | 0.07 | 0.86 | 19 | -0.04 | 0.18 | 0.40 |
| Categories (Z-score) | 36 | -0.18 | 0.08 | 21 | 0.32 | 0.42 | 17 | -0.08 | -0.19 | 19 | -0.20 | 0.20 | 0.09 |
| *(ii) Other* | | | | | | | | | | | | | |
| Reaction time (milliseconds) | | | | | | | | | | | | | |
| Decision time | 35 | 356.37 | 341.86 | 21 | 309.48 | 297.95 | 18 | 302.78 | 291.22 | 16 | 360.75 | 334.44 | 316.75 |
| Movement time | 36 | 277.89 | 256.53 | 22 | 231.64 | 230.55 | 12 | 243.25 | 228.58 | 16 | 296.19 | 271.06 | 255.81 |
| Finger Tapping (per min.) | 17 | 287.47 | 332.12 | 19 | 358.05 | 376.00 | 9 | 341.67 | 342.78 | 7 | 260.71 | 337.57 | 351.14 |
| WAIS Digit Symbol (raw) | 35 | 49.94 | 57.29 | 23 | 62.09 | 63.04 | 17 | 62.29 | 64.41 | 19 | 46.00 | 55.05 | 53.84 |
| Threshold task (score) | 31 | 2.09 | 1.89 | 22 | 1.85 | 1.83 | 14 | 1.83 | 1.74 | 17 | 2.08 | 1.98 | 1.95 |
| PASAT (out of 60) | 32 | 32.88 | 39.31 | 21 | 33.10 | 42.43 | 5 | 45.80 | 46.80 | 17 | 32.18 | 37.24 | 37.88 |
| *Visual spatial task* | | | | | | | | | | | | | |
| WAIS blocks (raw score) | 23 | 37.39 | 40.17 | 21 | 36.76 | 39.43 | 8 | 39.13 | 36.38 | 6 | 34.83 | 38.00 | 41.17 |
| *Mood* | | | | | | | | | | | | | |
| Log(CES-D) | 36 | 1.24 | 1.19 | 21 | 0.75 | 0.62 | 14 | 0.80 | 0.87 | 19 | 1.27 | 1.17 | 1.15 |
| Anxiety: Trait | 34 | 46.56 | 43.21 | 20 | 33.65 | 32.95 | 17 | 42.18 | 40.65 | 18 | 46.78 | 42.39 | 37.78 |
| Anxiety: Log(State) | 37 | 1.62 | 1.59 | 20 | 1.50 | 1.48 | 17 | 1.57 | 1.55 | 19 | 1.61 | 1.57 | 1.57 |
| Symptoms: Log(that week) | 37 | 1.47 | 1.36 | 21 | 0.73 | 0.72 | 14 | 0.65 | 0.82 | 19 | 1.54 | 1.40 | 1.33 |
| Symptoms: Log(now) | 37 | 1.10 | 0.90 | 21 | 0.35 | 0.57 | 17 | 0.75 | 0.49 | 17 | 1.13 | 0.96 | 1.01 |
| Fatigue | 36 | 3.25 | 4.19 | 20 | 6.25 | 6.80 | 17 | 5.71 | 6.29 | 18 | 3.06 | 4.28 | 4.33 |

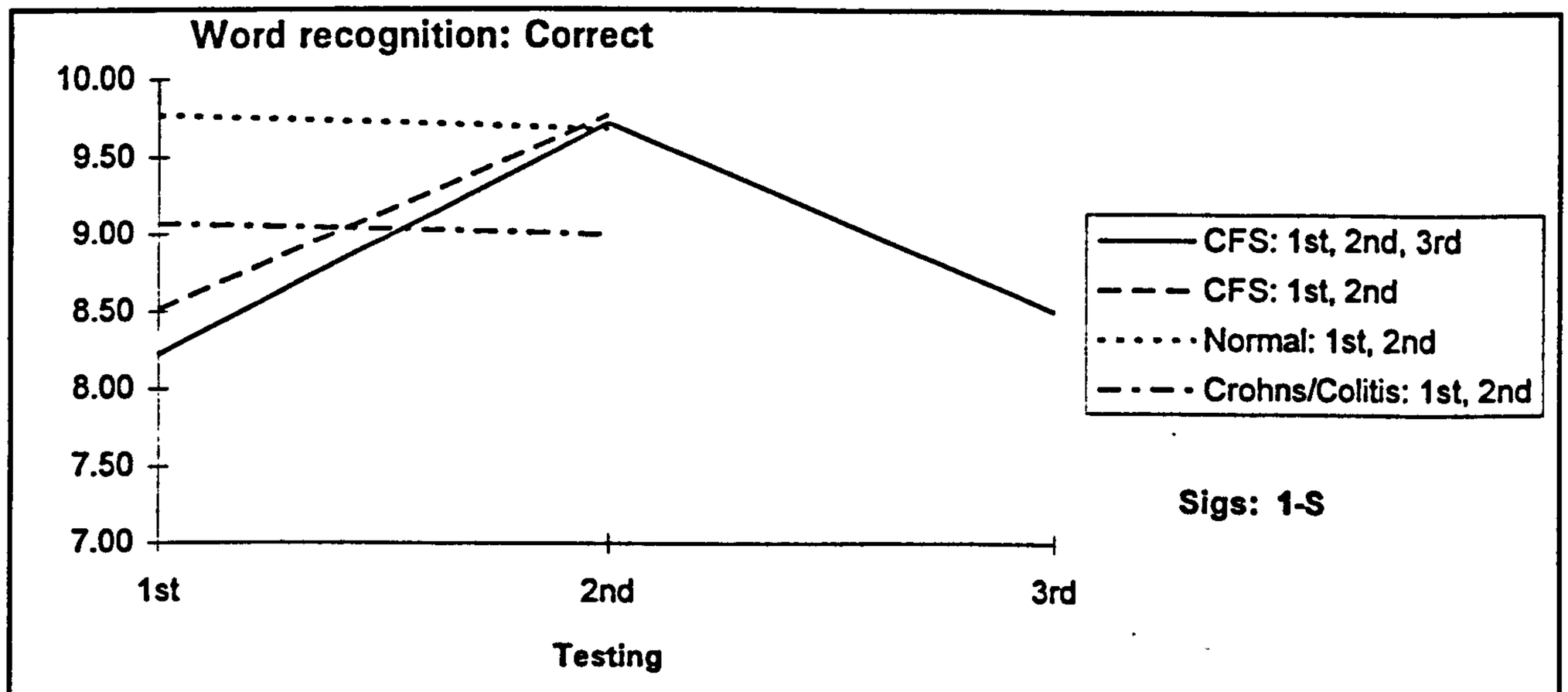
Graph 1



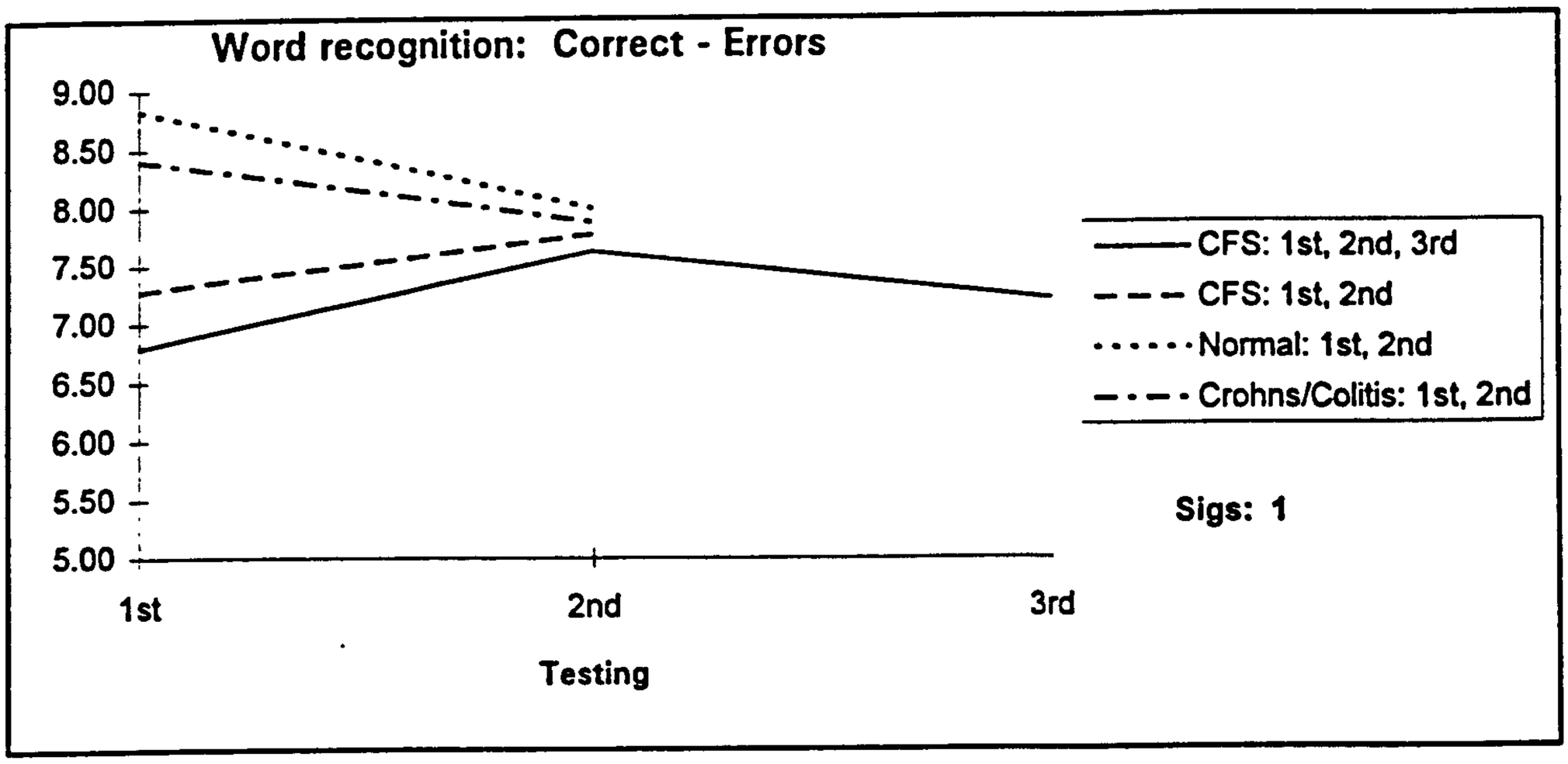

Graph 2



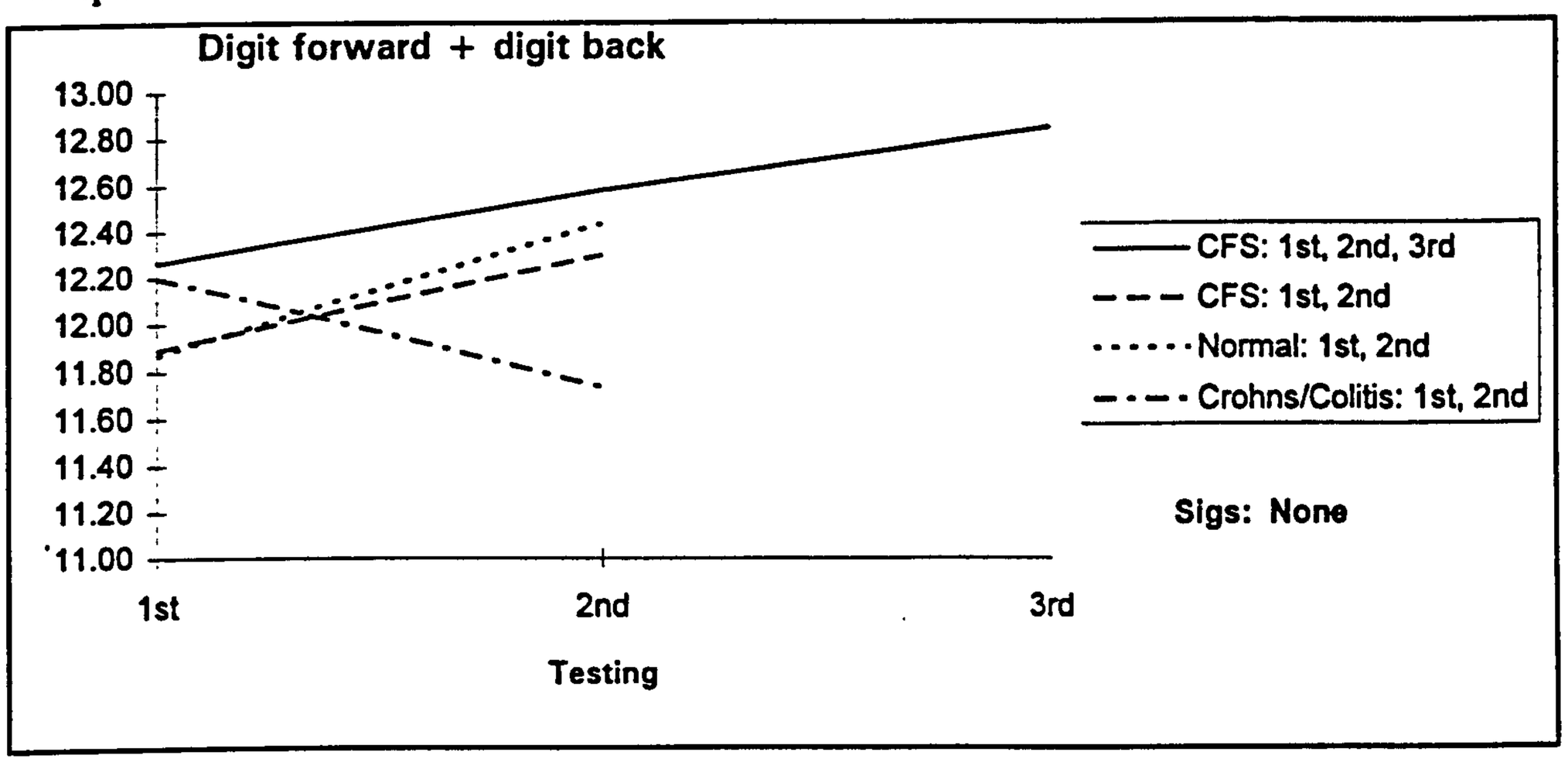

Graph 3



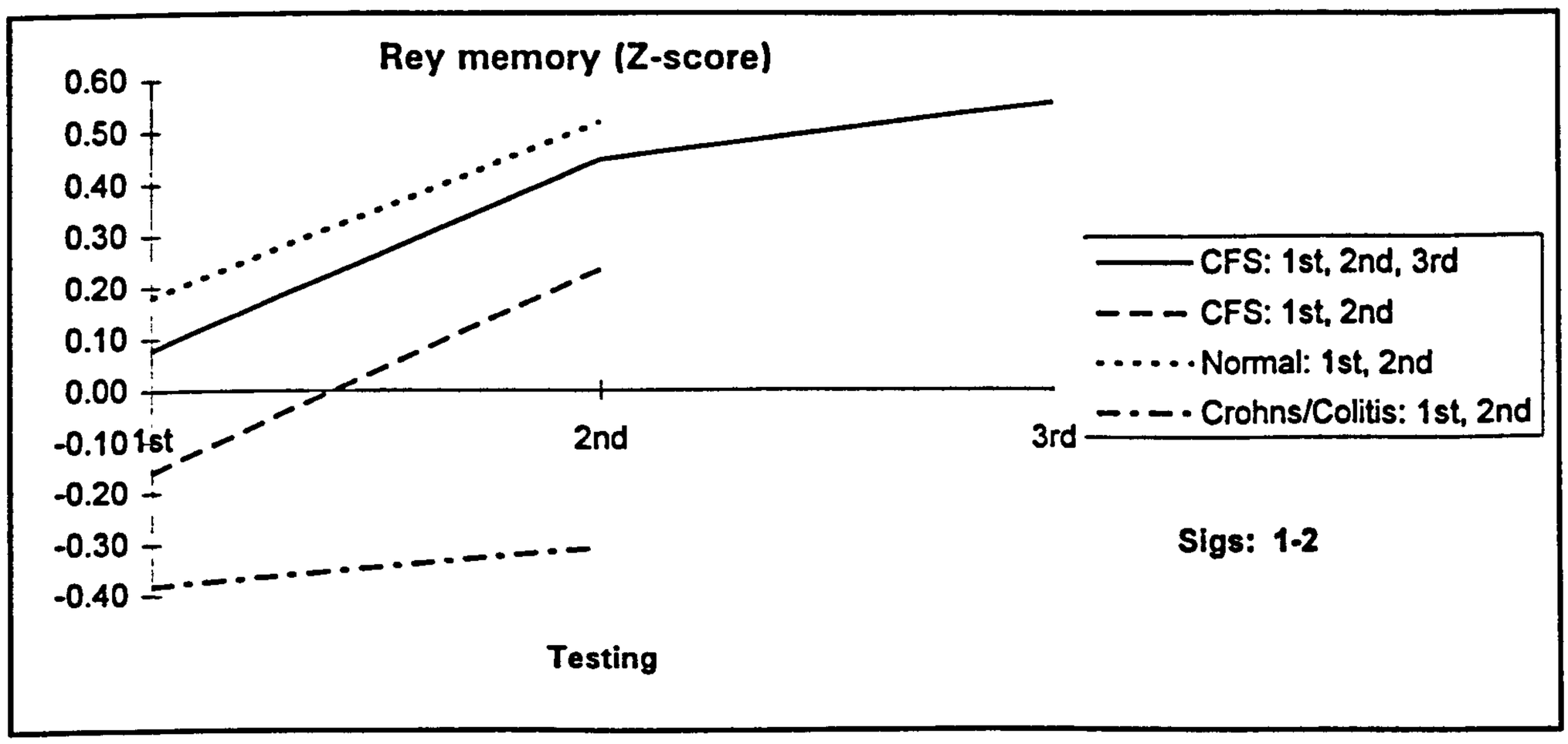
Graph 4



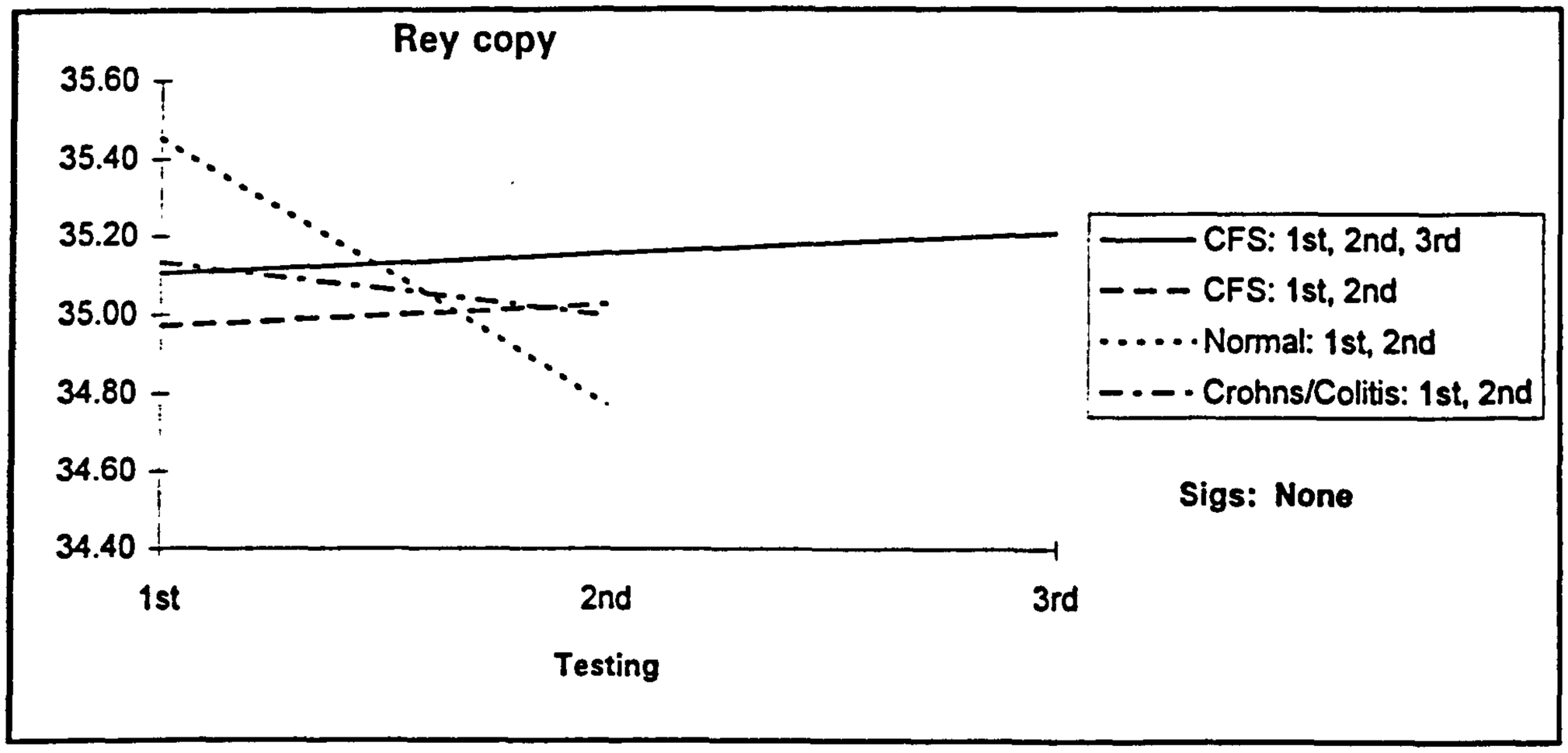

Graph 5



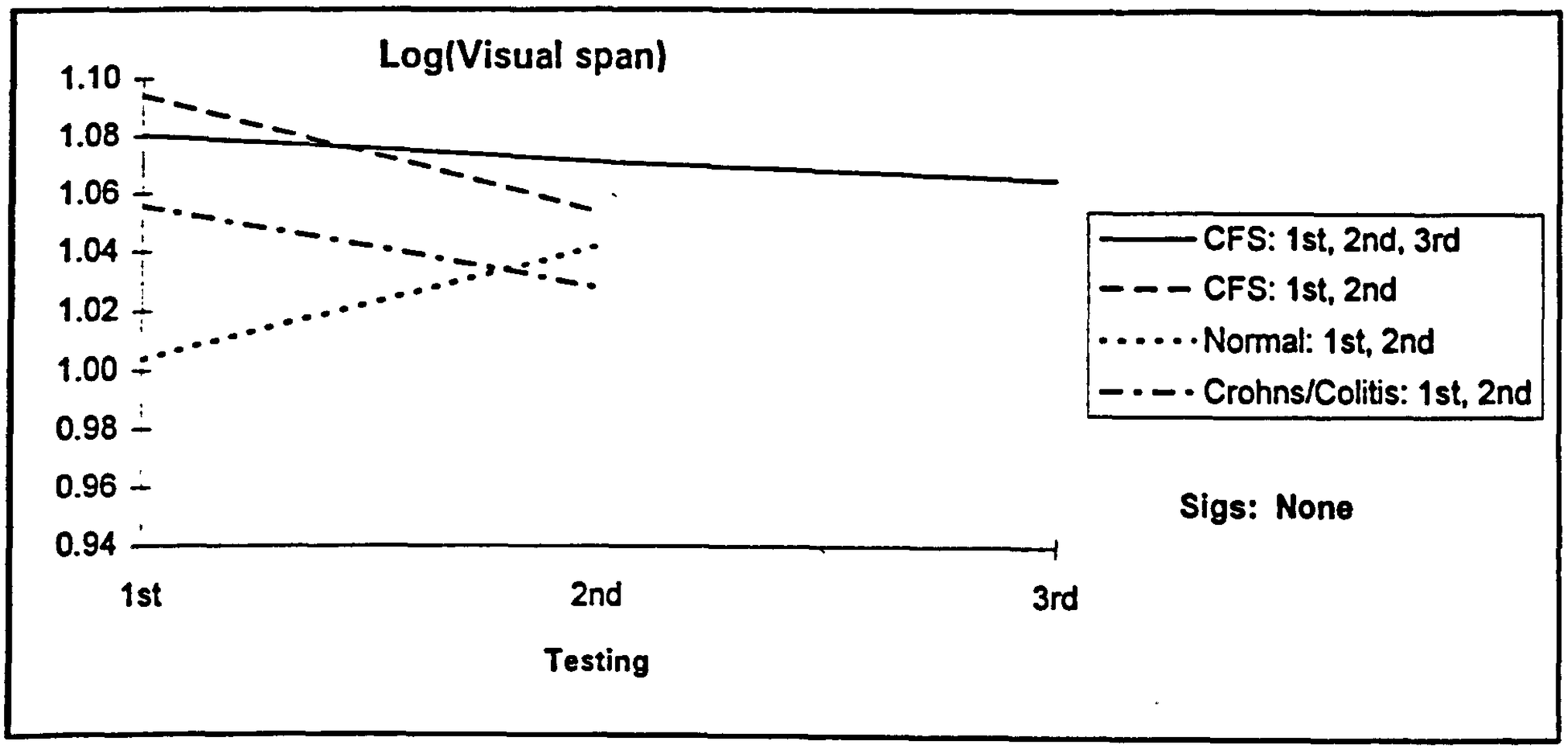

Graph 6



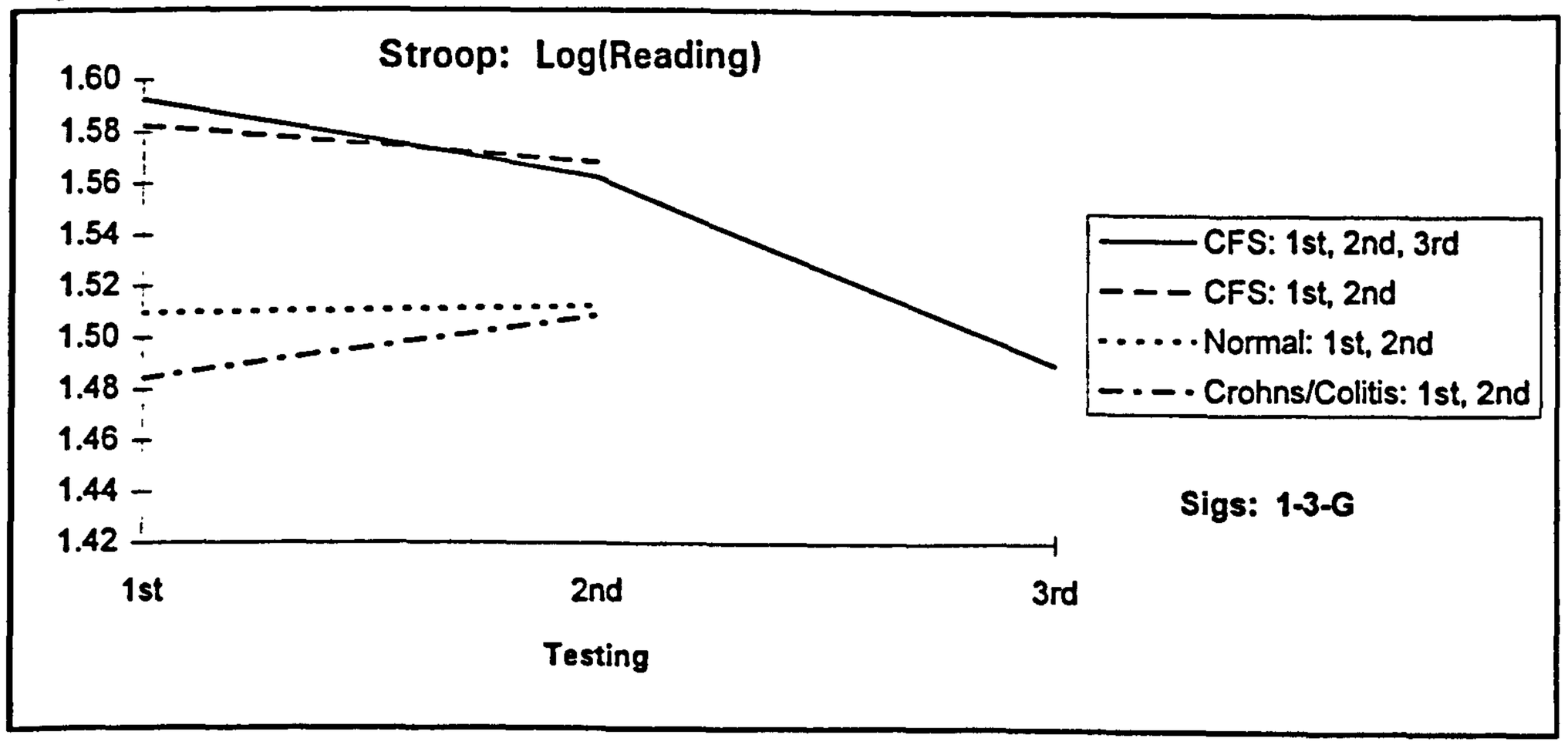
Graph 7



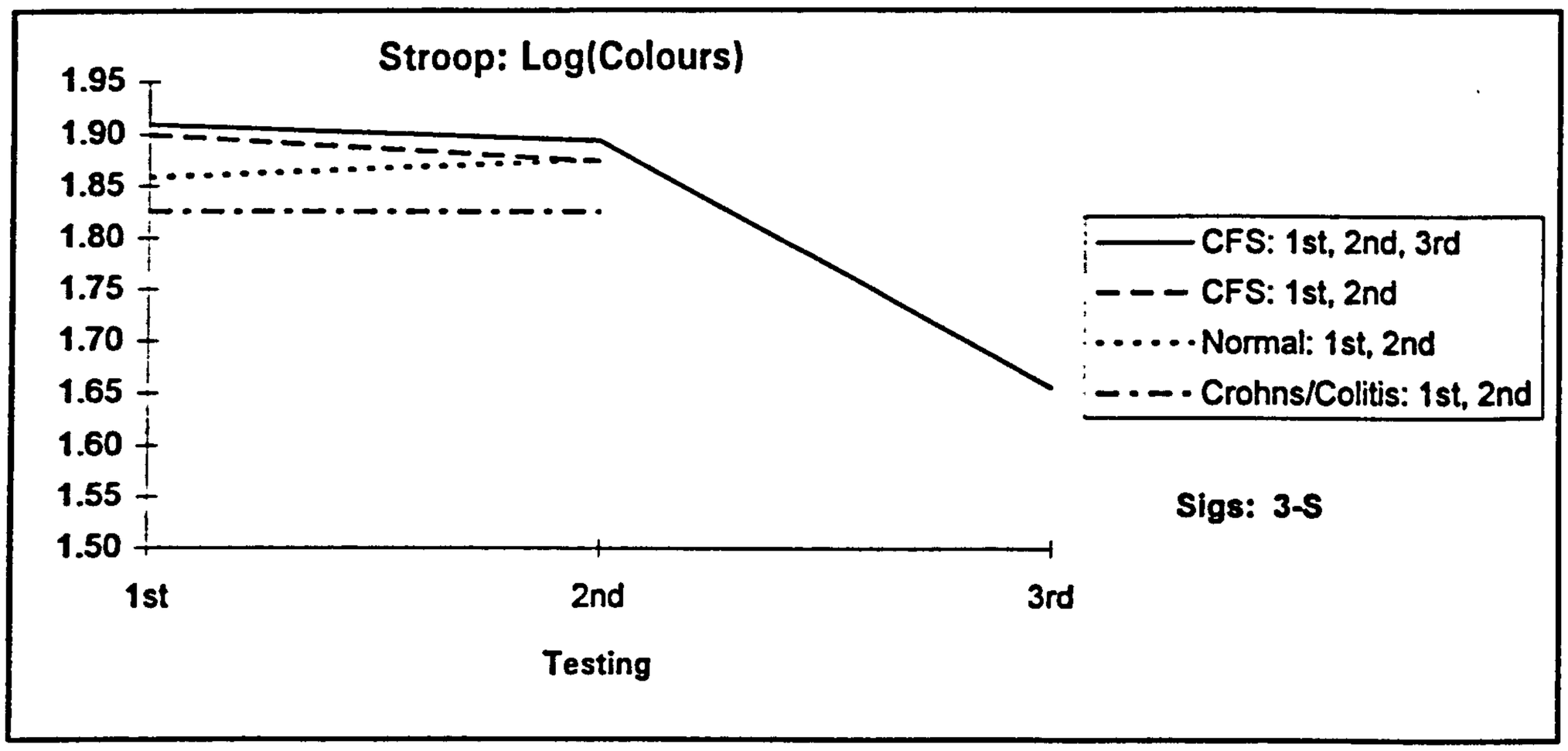

Graph 8



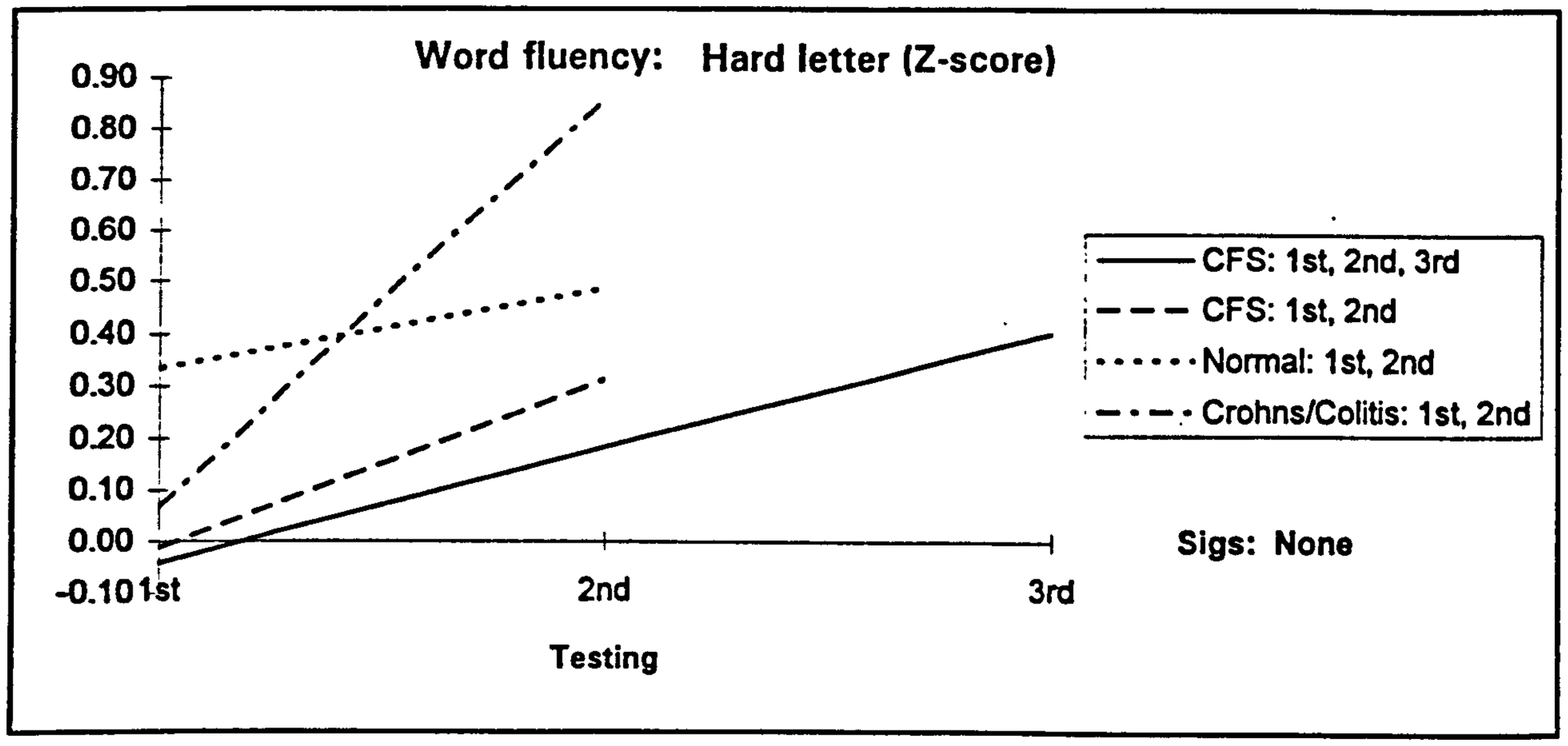

Graph 9



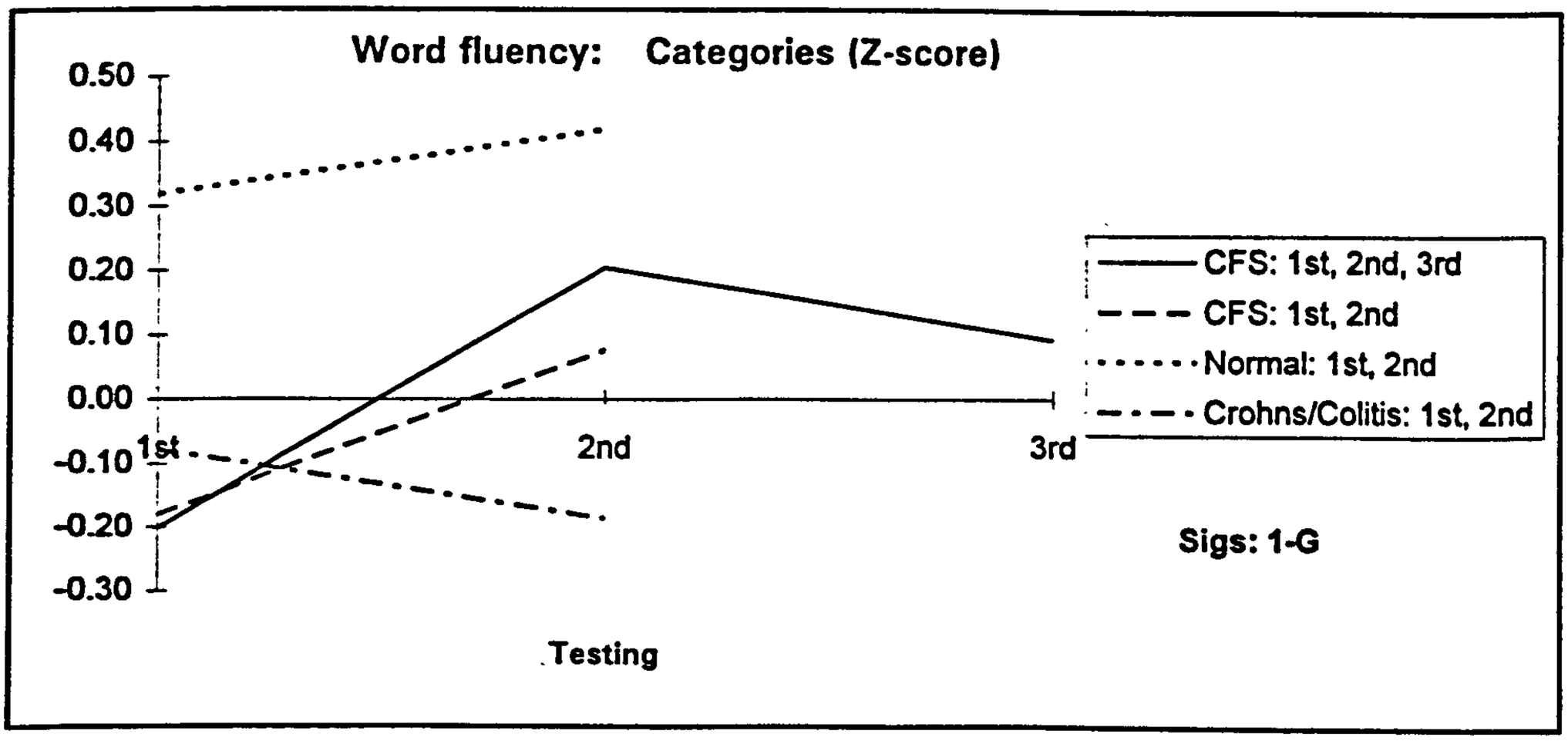
Graph 10



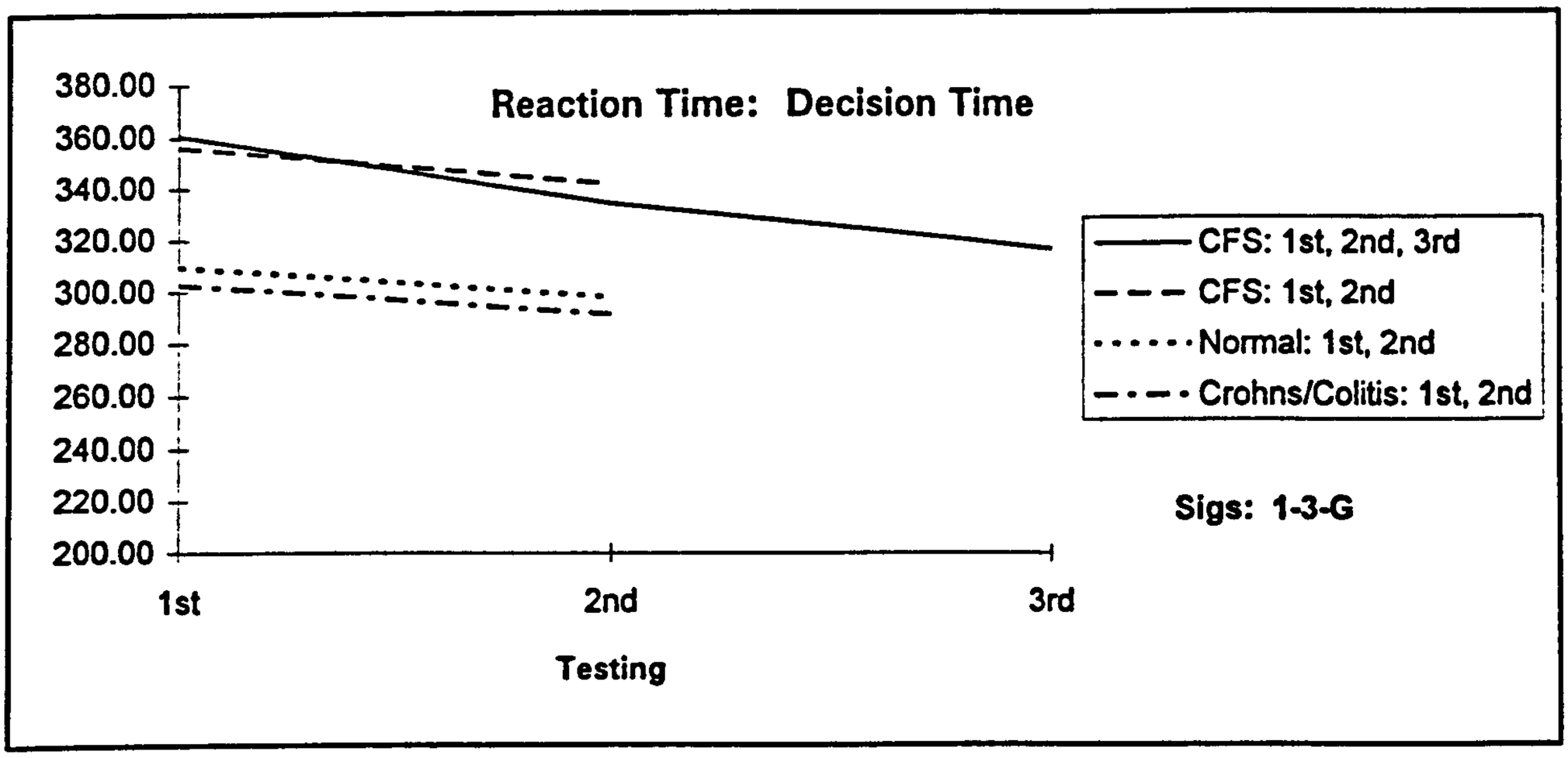

Graph 11



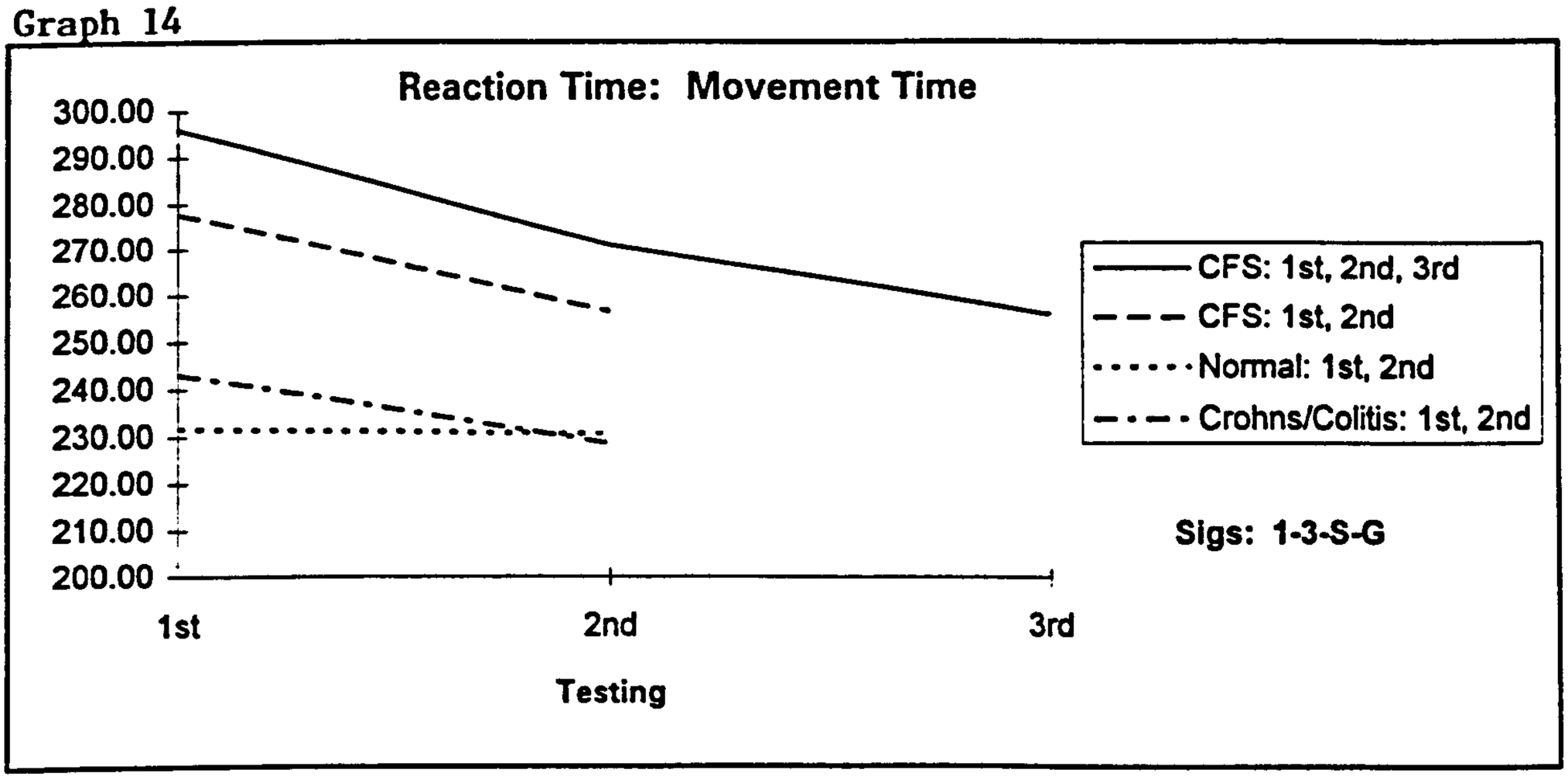

Graph 12



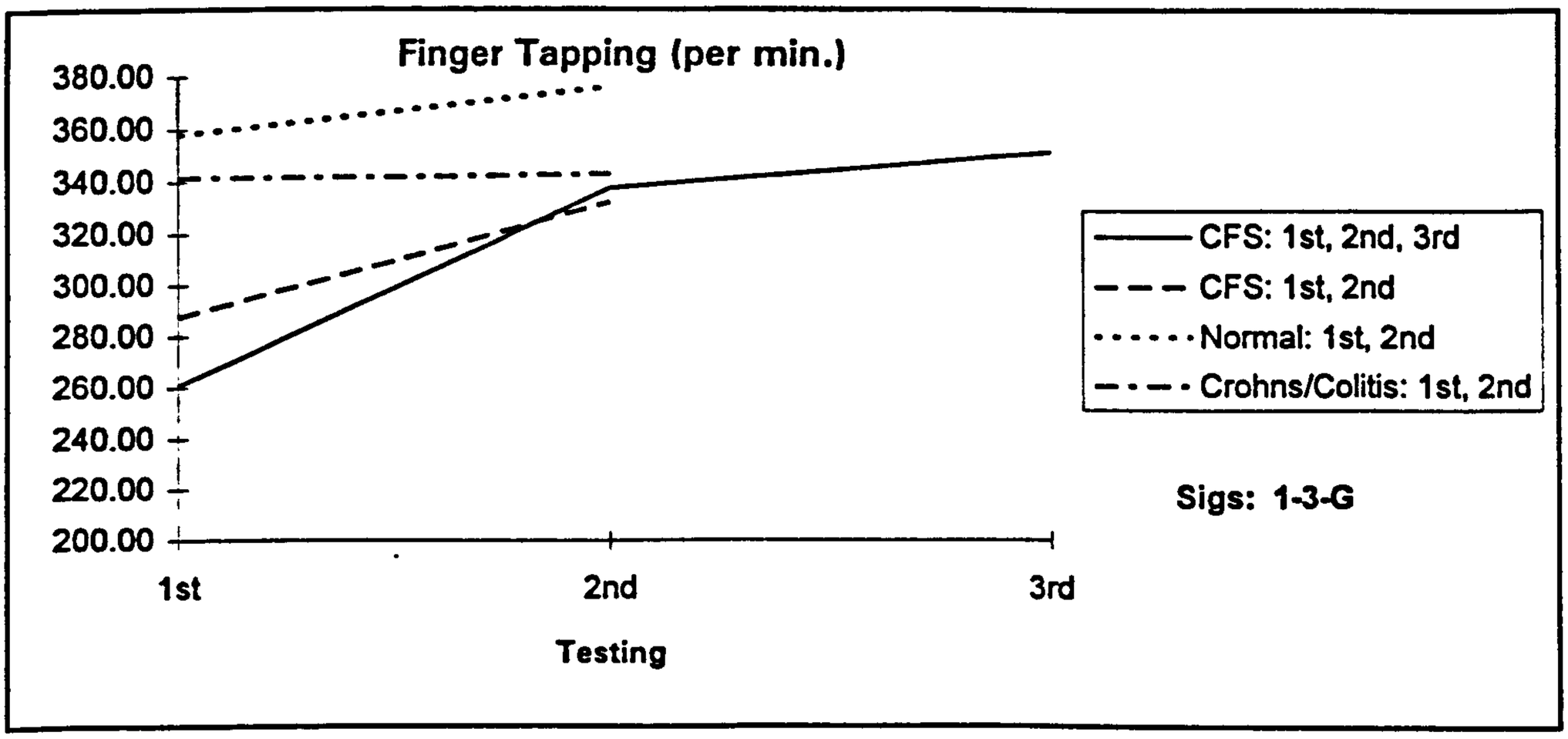
Graph 13



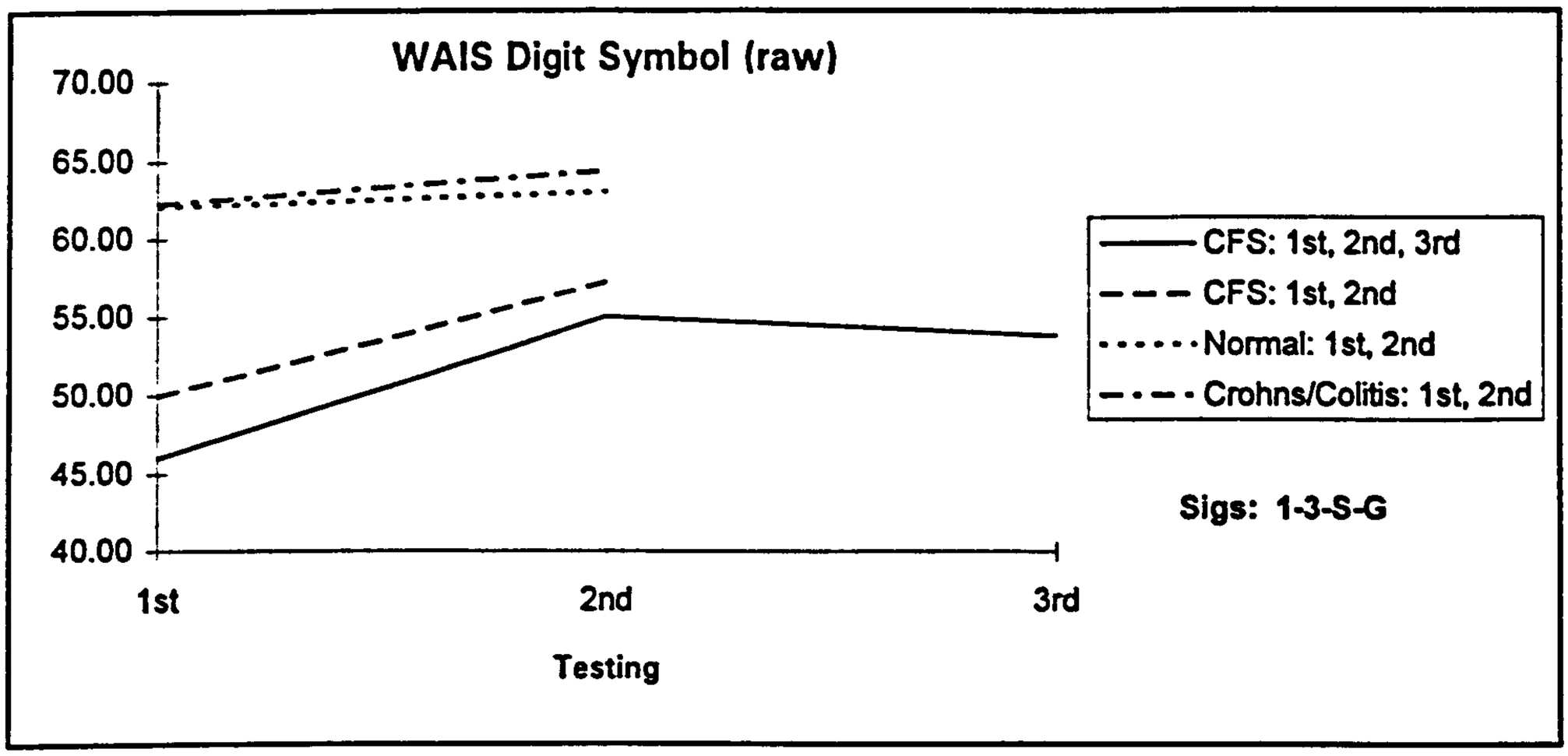

Graph 14



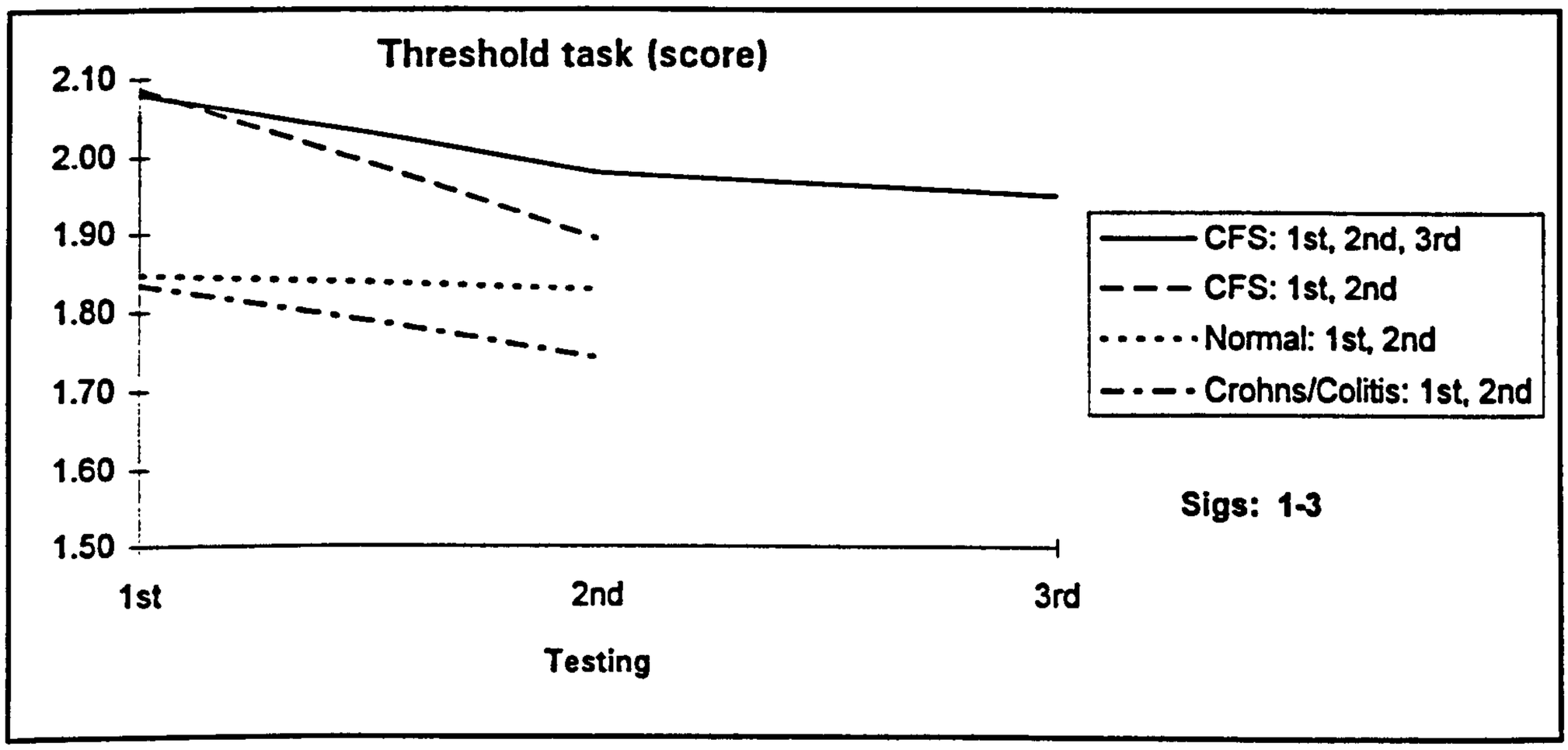

Graph 15



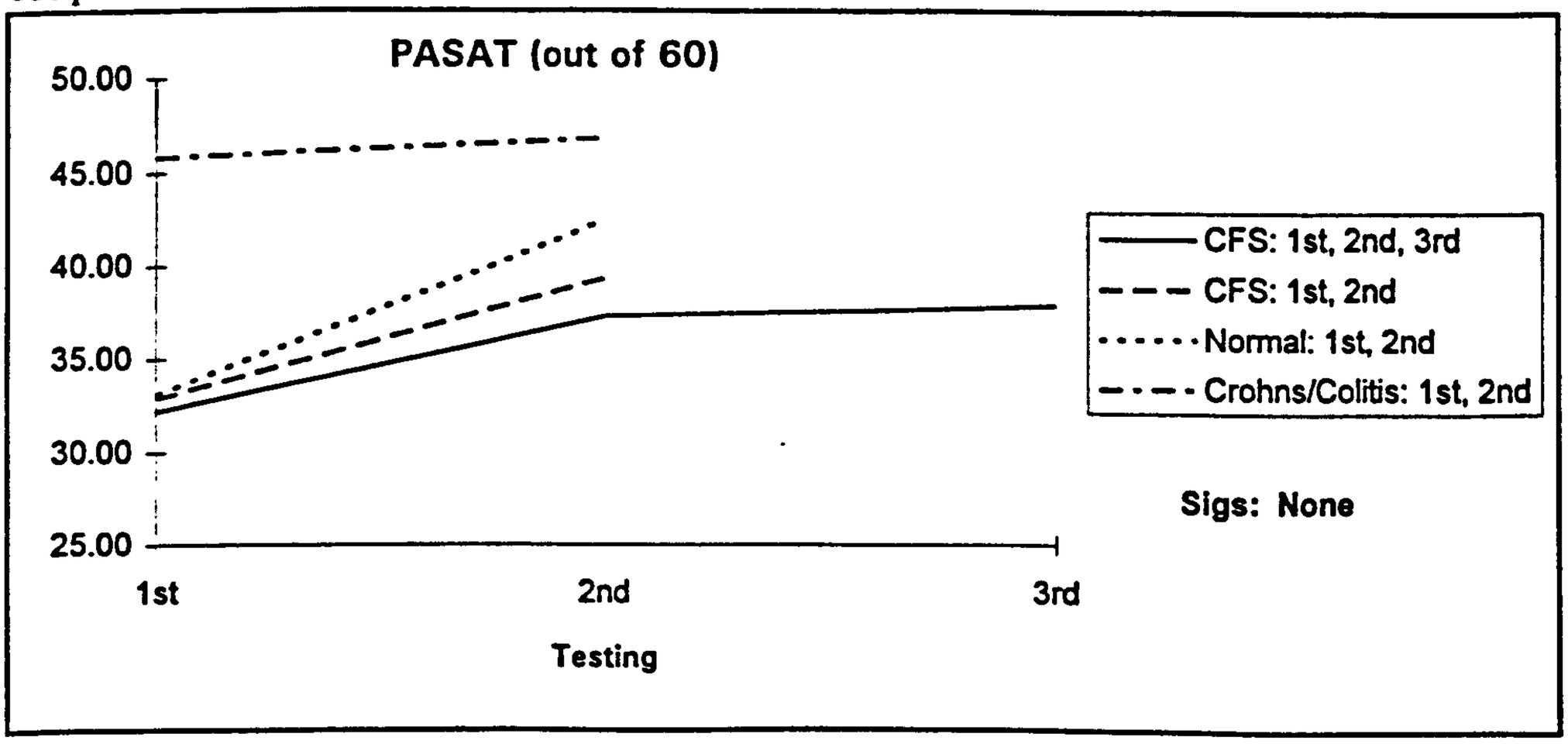
Graph 16



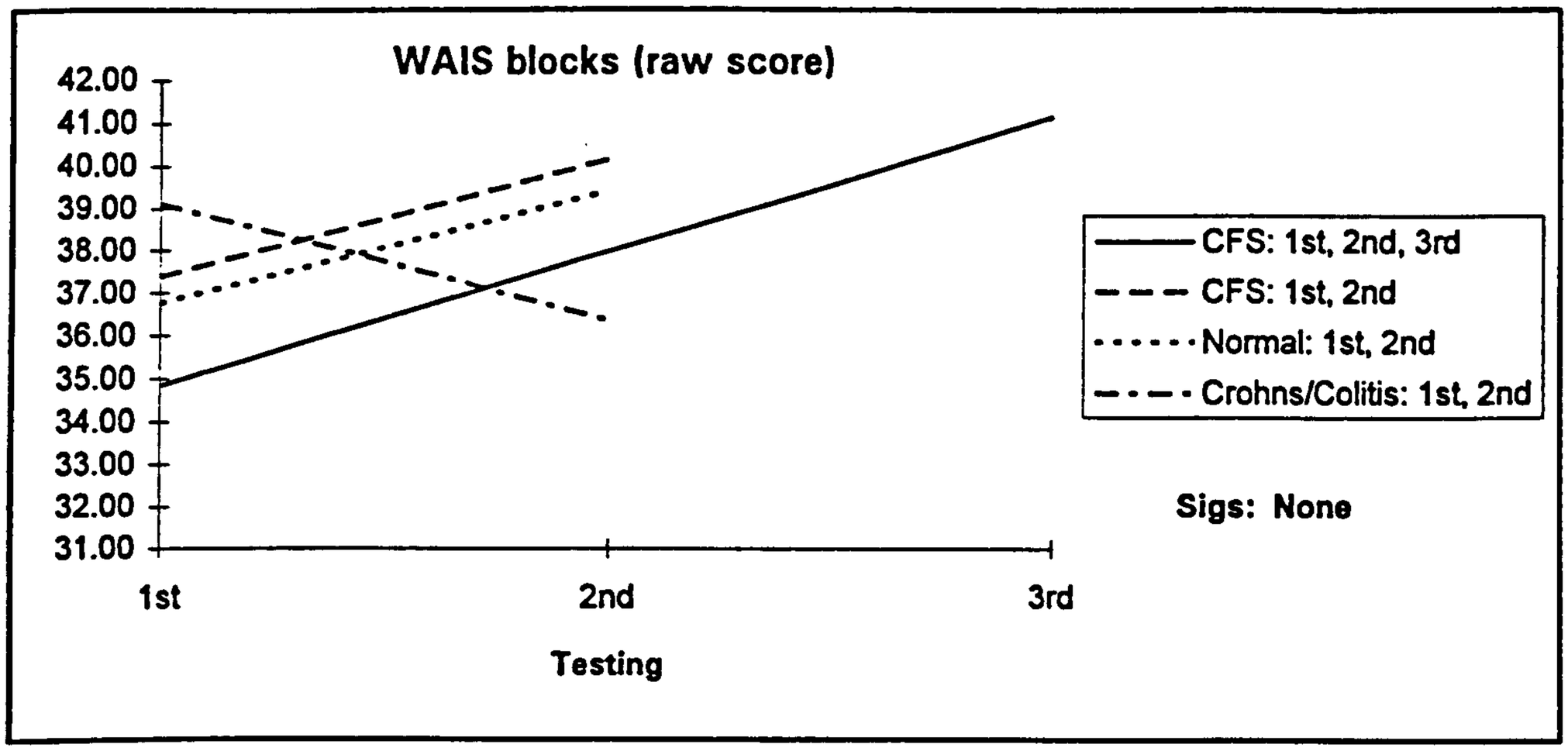

Graph 17



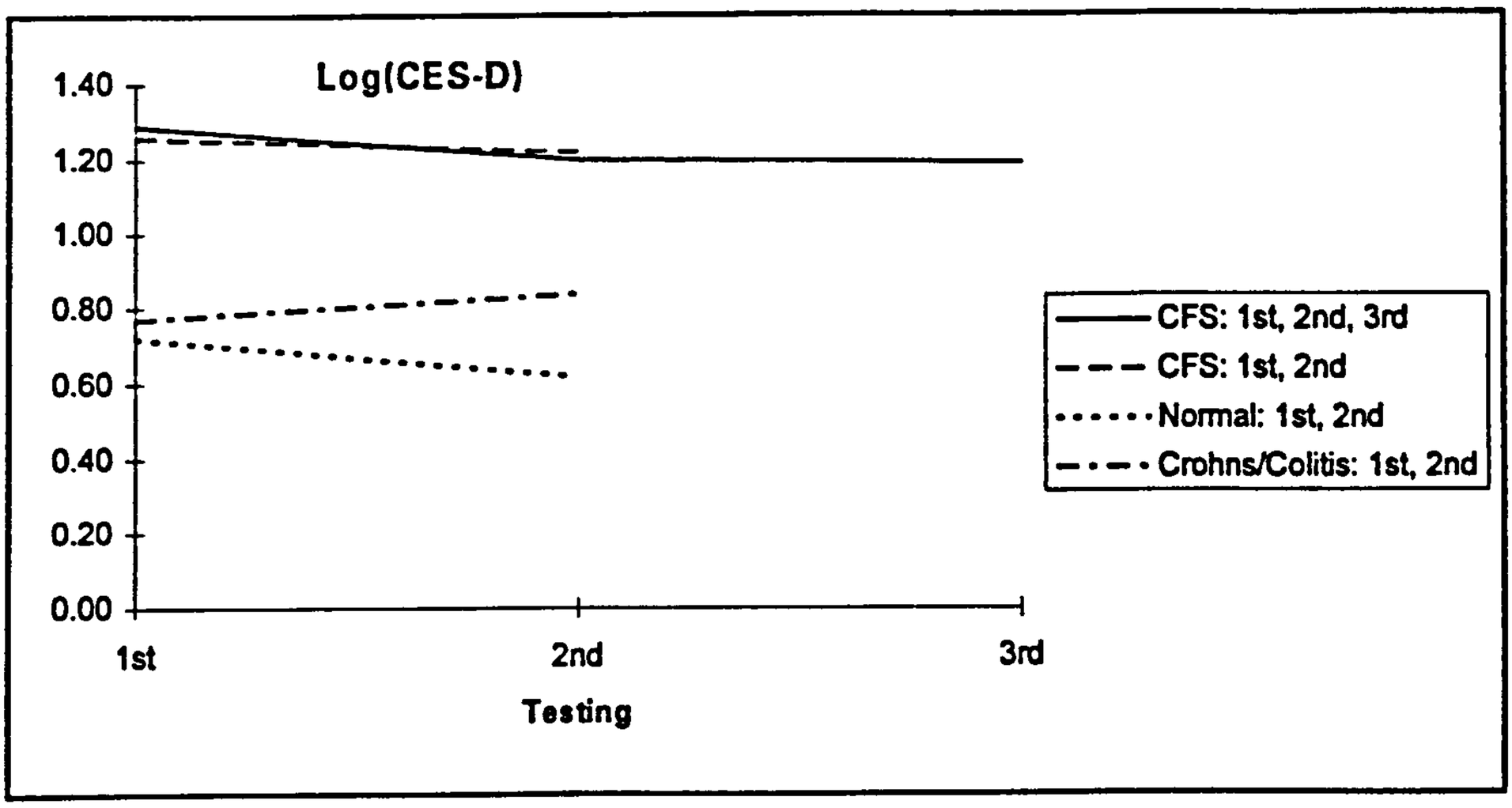

Graph 18



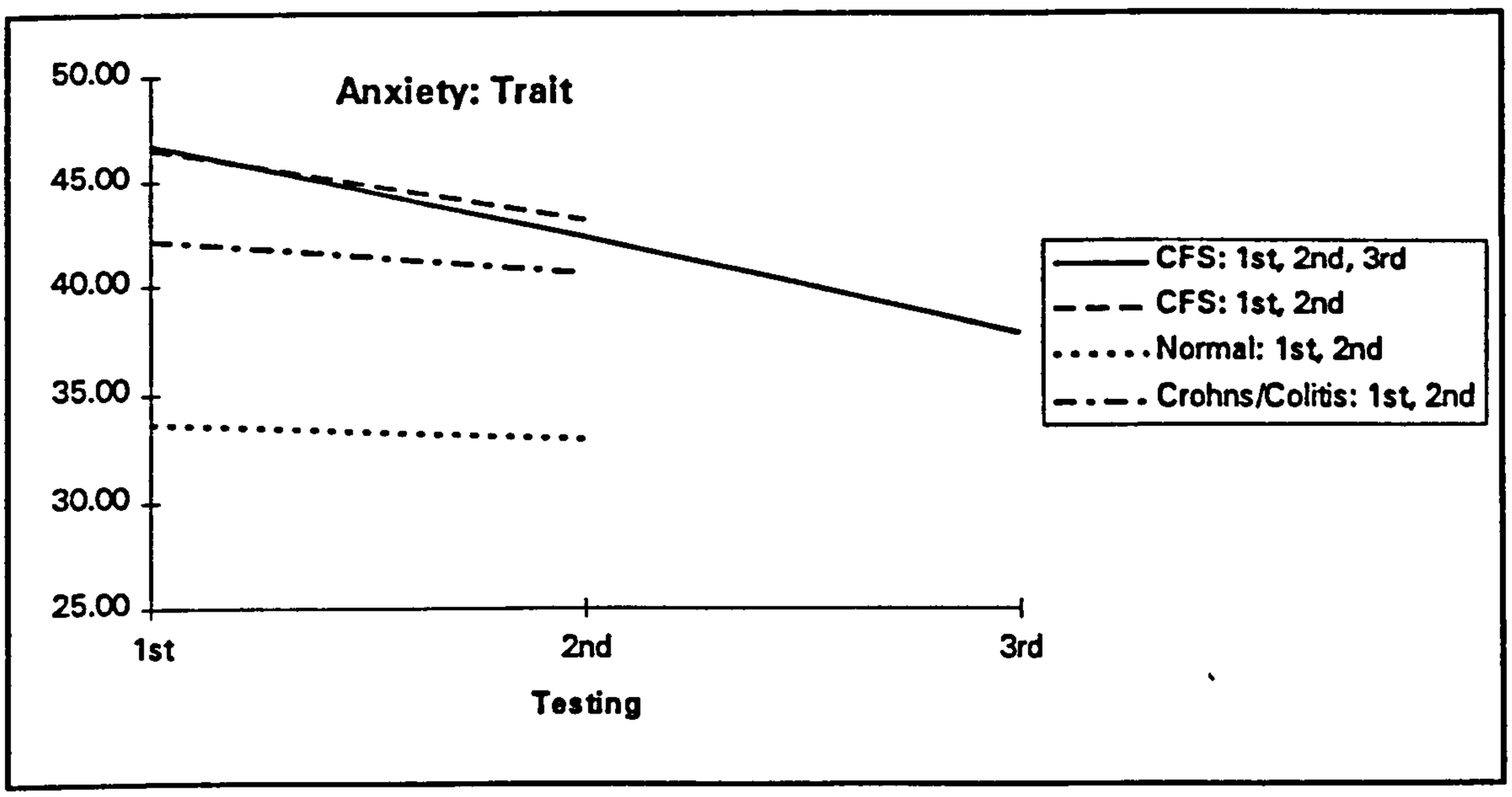
Graph 19


WAIS blocks (raw score)
42.00
41.00
40.00
39.00
38.00
37.00
36.00
35.00
34.00
33.00
32.00
31.00
1st
2nd
3rd
Testing
CFS: 1st, 2nd, 3rd
CFS: 1st, 2nd
Normal: 1st, 2nd
Crohns/Colitis: 1st, 2nd
Sigs: None

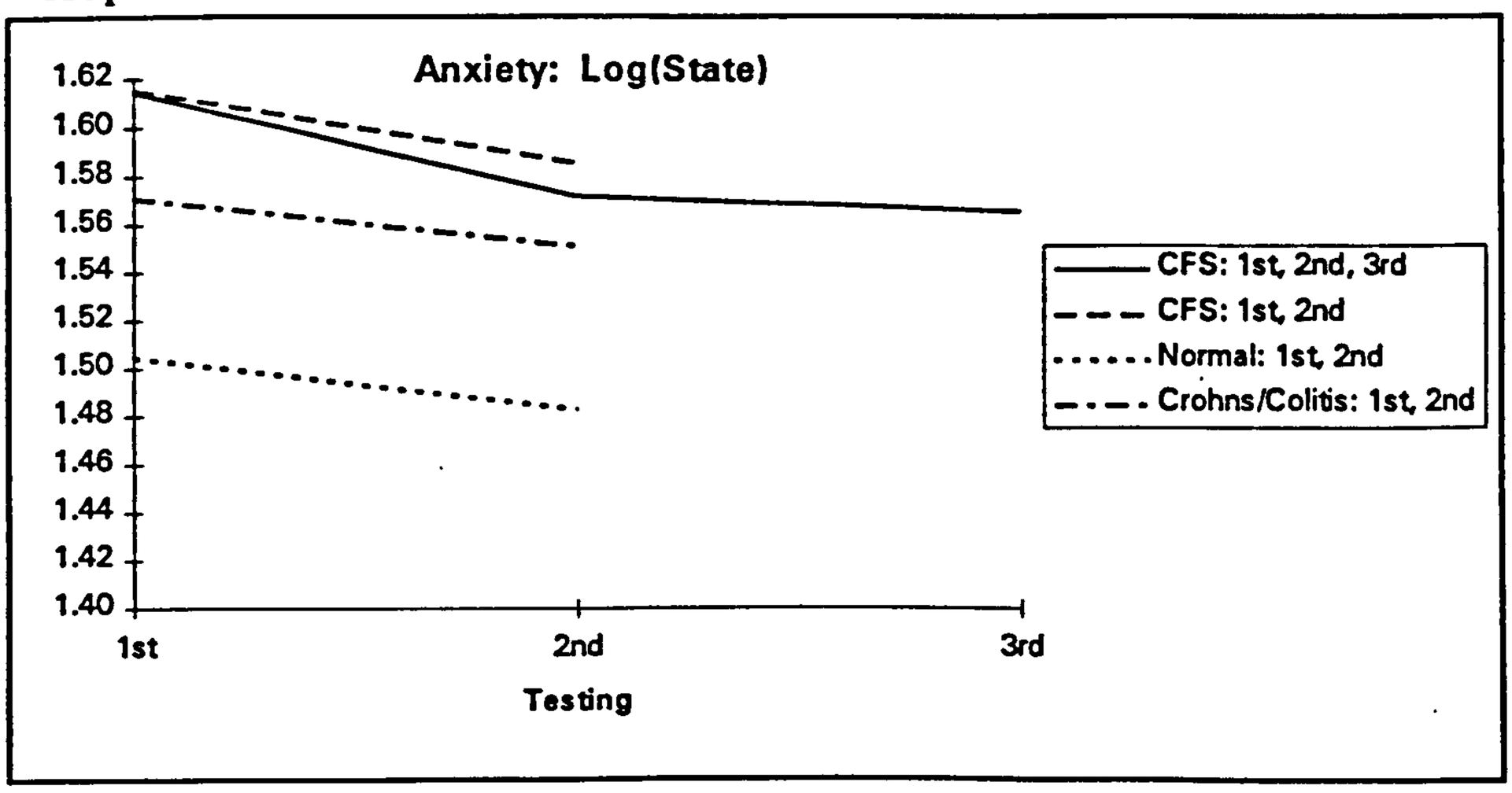
Graph 20



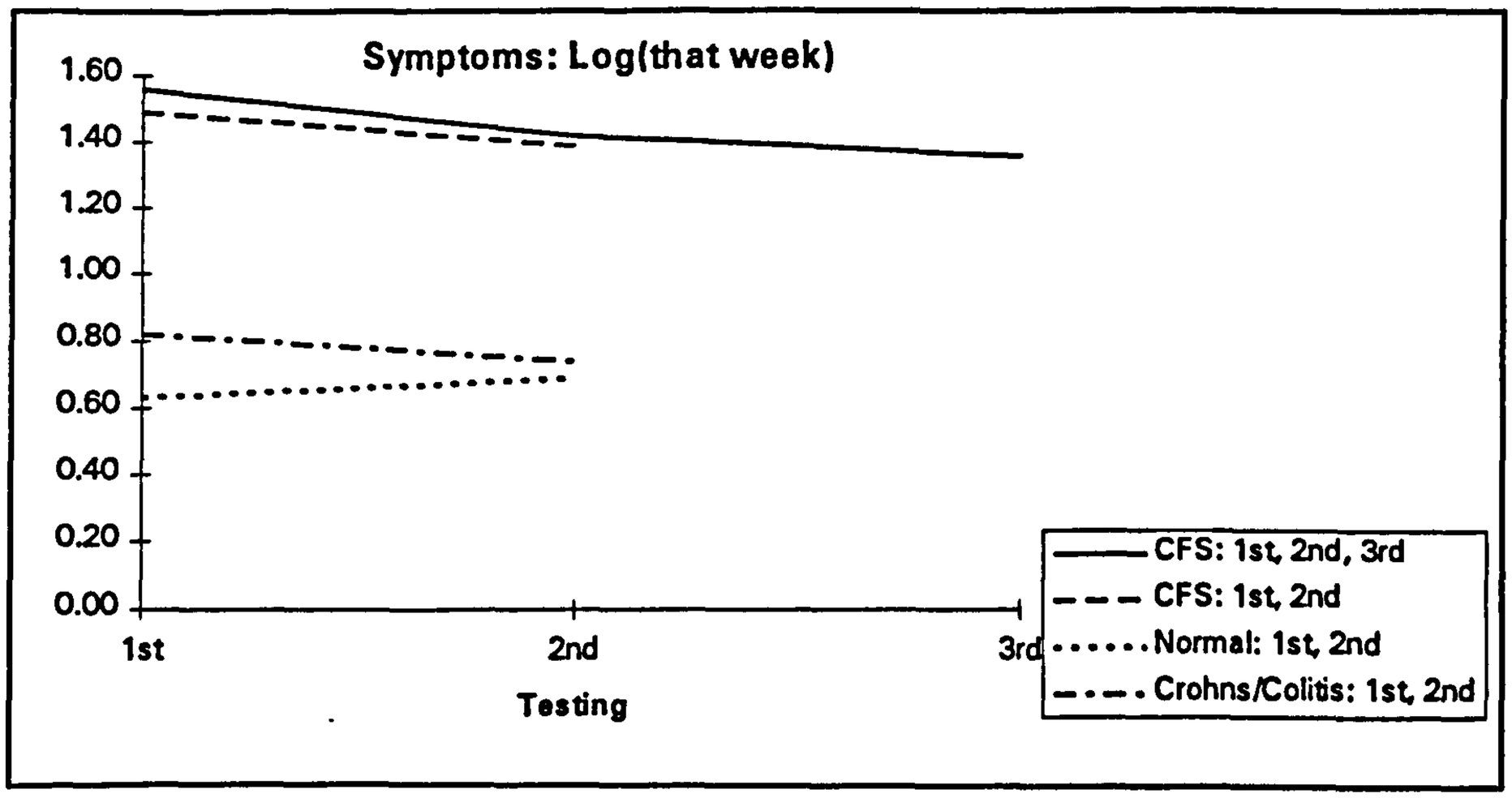

Graph 21



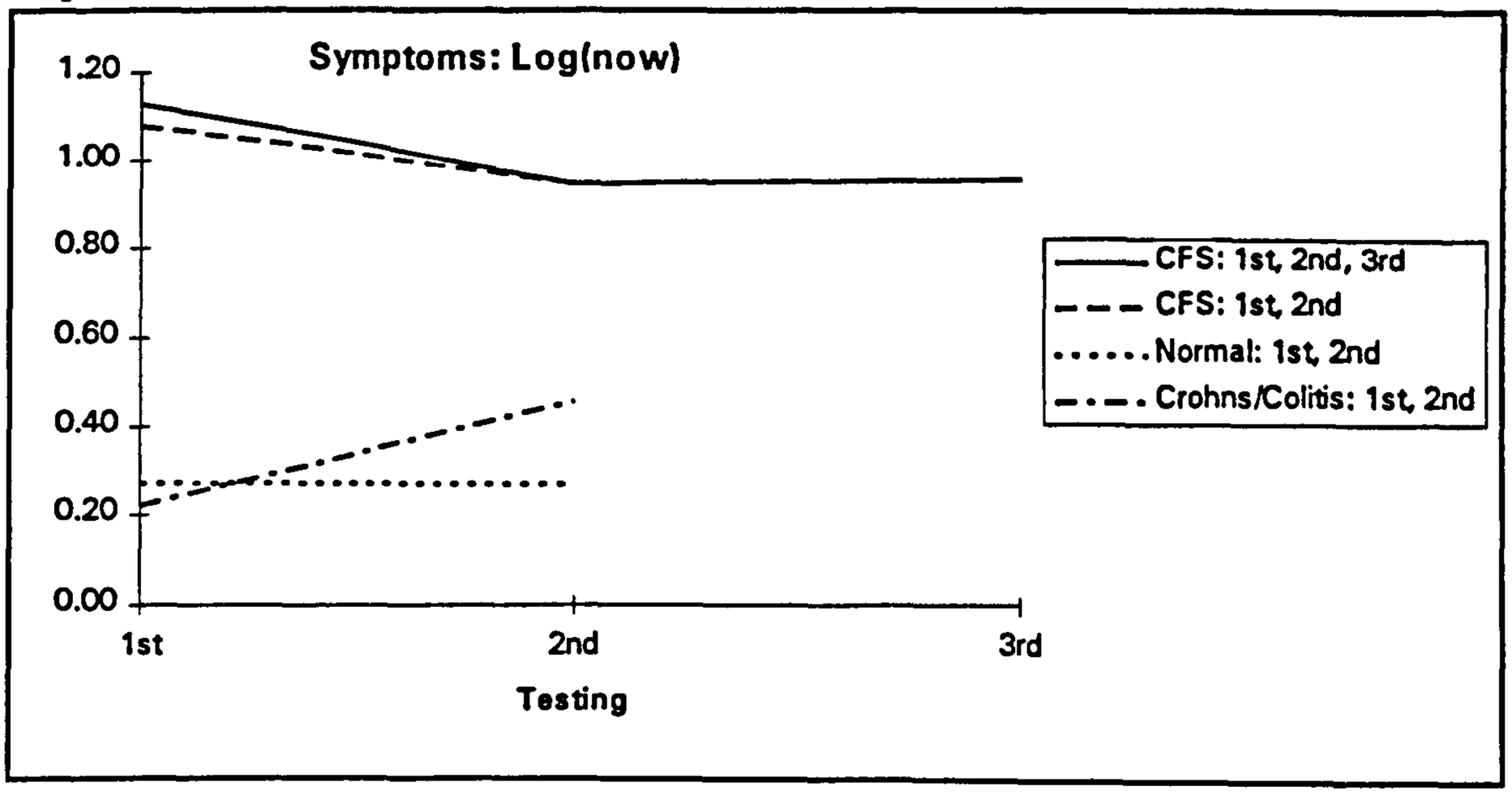

Graph 22



Graph 23




Graph 24




Graph 25