Illustrations of research findings and informed medical opinion about ME / ICD-CFS which psychiatrists of the Wessely School seem to dismiss, trivialise or completely ignore

These illustrations (from the large number available) are taken almost entirely from Denigration by Design? Volumes I and II by Eileen Marshall and Margaret Williams, both volumes of which address the role played in the present perception (medical and public) of myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) by Simon Wessely, currently Professor of Liaison and Epidemiological Psychiatry at Guy's, King's and St Thomas' Medical School, London, where he is also Director of the Chronic Fatigue Research Unit. Copies are available from DM Jones: telephone (UK) 0208-554-3832). Volume I covers the period 1987-1996 (217 pages) and Volume II covers the period 1996-1999 (271 pages). These volumes consider some of the international biomedical research findings on ME/ICD-CFS off-set against many quotations from the published papers of adherents to the Wessely School of psychiatry, thus affording the reader an opportunity to decide if the psychiatric dogma about ME and CFS as promoted by these doctors lacks scientific credibility in the light of the known biomarkers of an organic pathoaetiology.

1955

Outbreak at the Royal Free ED Acheson (who later became Sir Donald Acheson, UK Chief Medical Officer). *Lancet 1955:394-395*

"All outbreaks have been remarkable for …the relatively long active course of the disease…and for marked muscular pain and spasm".

1956

A new clinical entity? Editorial; *Lancet 1956 (May 26);789-790*. (Although at the time this Editorial was anonymous, it was later admitted by Sir Donald Acheson that he had written it).

"In spite of perplexing variations in the clinical picture from case to case…it soon became clear…that a new clinical entity had appeared"

"Relapses are frequent"

"Among the more characteristic features…are the severe muscular pains, often accompanied by exquisite tenderness"

"We believe that its characteristics are now sufficiently clear to differentiate it from, need it be said, hysteria".

1959

The clinical syndrome variously called benign myalgic encephalomyelitis, Iceland Disease and Epidemic Neuromyasthenia. ED Acheson. *Am J Med 1959:26:569-595*

"Pain in the muscles was an almost constant feature…in severe cases it was agonizing and unresponsive even to opiates"

"Definite parasthesia occurred…diplopia (was noted)"

"It would be manifestly erroneous to consider as hysteria the emotional instability associated with this illness…the disorder is not a manifestation of hysteria"

"Other sensory disturbances consisted of loss of memory and difficulty in concentration"

"It is concluded that the disease is recognizable in its epidemic form on clinical and epidemiological grounds and therefore may properly be considered a clinical entity".

1970

Encephalomyelitis resembling benign myalgic encephalomyelitis. SGB Innes
Lancet 1970: (May 9):969

"Motor weakness may not be confirmed on formal testing since it appears to take the form of an incapacity for sustained muscular effort".

1977

Iceland Disease (benign myalgic encephalomyelitis or Royal Free disease) AM Ramsay, EG Dowsett et al *BMJ 1977: (May 21):1350*

"Objective manifestations of the disease can still be present over thirty years after the initial illness".

1978

Epidemic myalgic encephalomyelitis Editorial *BMJ 1978: (3 June):1436-1437*

"The features common to every epidemic include headache, unusual muscular pains (which may be severe), lymphadenopathy and low grade fever. In a minority of cases frank neurological signs can be detected by careful clinical examination: there may be

nystagmus, diplopia, myoclonus, bulbar weakness, motor weakness, increased or decreased tendon reflexes, disturbances of the sphincters and extensor plantar responses. Fasciculations, cranial nerve lesions and extrapyramidal signs have also been reported. One characteristic feature of the disease is exhaustion, any effort producing generalised fatigue. Often there (is) emotional instability and lack of concentration. The clinical outcome may take any of three courses: some patients recover completely, some follow a relapsing course and some are permanently incapacitated"

"At a symposium held recently at the Royal Society of Medicine to discuss the disease and plan research there was clear agreement that myalgic encephalomyelitis is a distinct nosological entity"

"Other terms that have been used to describe the disease were rejected as unsatisfactory for various reasons: the cardinal clinical features show that the disorder is an encephalomyelitis…indeed, the exhaustion and tiredness are similar to that described by patients with multiple sclerosis"

"From the patient's point of view the designation 'benign' is misleading, since the illness may be devastating"

"Some authors have attempted to dismiss this disease as hysterical, but the evidence now makes such a tenet unacceptable…the organic basis is clear --- from the detection of an increased urinary output of creatine, the persistent findings of abnormal lymphocytes in the peripheral blood of some patients, the presence of lymphocytes and an increased protein concentration in the cerebrospinal fluid…and the neurological findings. Immunological studies showed a high incidence of serum anticomplementary activity and the presence of ill-defined aggregates on electron microscopy of acute=phase sera".

(This Editorial was fully referenced to support the claims made).

<u>An outbreak of encephalomyelitis in the Royal Free Hospital Group, London, in 1955</u>
Nigel Dean Compston *Postgraduate Medical Journal 1978:54:722-724*

"It became clear early on…that there was organic involvement of the central nervous system…there was objective evidence of involvement (of the CNS)"

"The most characteristic symptom was the prolonged painful muscle spasms"

"Bladder dysfunction occurred in more than 25% of all the patients"

"Objective evidence of brain stem and spinal cord involvement was observed"

"McEvedy and Beard's (psychiatric) conclusions ignore the objective findings".

1979

Clinical and biochemical findings in ten patients with benign myalgic encephalomyelitis
AM Ramsay; A Rundle *Postgraduate Medical Journal 1979:55:856-857*

"Ten patients…were investigated for blood levels of myoglobin and various enzymes…the biochemical pattern bears a close similarity to that found in Duchenne muscular dystrophy (DMD). These findings are discussed with particular reference to the recent suggestion that the permeability of cell membranes may be impaired by changes in intracellular energy mechanisms"

"The dominant clinical features could be classified as follows: (1) abnormal muscle fatigability (with severe pain, particularly in the legs and back)…(2) Circulatory impairment was a feature of all cases…suggestive of hypothalamic damage (and)
(3) Impairment of memory and inability to concentrate was common in all patients"

"The duration of illness in the ten cases was 35 years, 9 years, 6 years, 3 years, 2 years, 23 years, 17 years, 2 years, 5 years and 17 years respectively. A tendency to severe relapse was a feature of (four) cases"

"If the aetiological factor in benign myalgic encephalomyelitis impairs the permeability of the muscle cell membrane as a result of changes in the intracellular energy content, this could be followed by a differential loss of intracellular proteins".

1984

Myalgic encephalomyelitis and the general pracitioner JC Murdoch *New Zealand Family Physician 1984:11:127-128*

" recent reports have shown an association with infection with the Coxsackie and two authoritative editorials have pointed to an entirely physical basis for the disorder"

"Most sufferers…had monumental problems with work, family and personal life and with their doctors. They should be warned to expect a long illness charaterised by relapses. They should be certified as unfit for work"

"In the long-term sufferer, patients are often anxious to identify food and chemical allergies".

1985

Persisting Illness and Fatigue in Adults with Evidence of Epstein Barr Virus Infection
Stephen E Straus et al *Annals of Internal Medicine 1985:102:7-16*

(Note that in the US, the condition was at that time thought to be associated with the Epstein Barr (glandular fever) virus and so was known as chronic EBV disease)

"By all regards, including formal evaluations, many of these patients appeared to be neurotic. However, our detailed studies have uncovered a series of subtle, yet objective, organic abnormalities in these patients"

"This disorder…is not rare"

"It is of immeasurable benefit to patients with this disorder to document an organic basis for their complaints".

The postviral fatigue syndrome – an analysis of the findings in 50 cases PO Behan, WMH Behan, Eleanor J Bell *Journal of Infection 1985:10:211-222*

"Our data confirm the organic basis of the illness (and) suggest that it is associated with disordered regulation of the immune system and persistent viral infection"

"The illness was severe, with a high morbidity and a disastrous effect on their lives".

Electrophysiological studies in the post-viral fatigue syndrome Goran A Jamal and Stig Hansen *JNNP 1985:48:691-694*

"The post-viral fatigue syndrome, also known as ME, has been recognised recently as a distinct neurological entity with increasing evidence of the organic nature of the disease"

"The most important findings were type II fibre predominance, subtle and scattered fibre necrosis and bizarre tubular structures and mitochondrial abnormalities"

"About 75% of the patients had definitely abnormal single fibre electromyography results. This was regarded as evidence of abnormality in the peripheral part of the motor unit"

"We conclude that we have shown clear electrophysiological evidence of an abnormality in the peripheral part of the motor end unit in patients with post-viral fatigue syndrome".

1987

The postviral fatigue syndrome: a review MI Archer *JRCGP 1987:37:212-216*

"However compelling the evidence for an hysterical basis may be, there is further, equally compelling evidence of organic disease".

Phenotypic and functional deficiency of natural killer cells in patients with Chronic Fatigue Syndrome Michael Caliguri, Dedra Buchwald, Paul Cheney, Daniel Peterson, Anthony L Komaroff et al *J Immunol 1987:139:3306-3313*

"When tested for cytotoxicity against a variety of different target cells, patients with CFS consistently demonstrated low levels of killing"

"These studies demonstrated that a majority of patients with CFS have low numbers of NKH1+T3- lymphocytes, a population that represents the great majority of NK (natural killer) cells for normal individuals…resulting in a quantitative and functional deficiency of this NK subset".

1988

Postviral fatigue syndrome PO Behan WMH Behan *Crit Rev Neurobiol 1988:4:2: 157-178*

"Any kind of muscle exercise can cause the patient to be almost incapacitated for some days afterward. In severe cases, the patient is usually confined to bed"

"Psychiatric diagnoses abound: many patients will already have been labelled as neurotic, neurasthenic, or depressed"

"What is certain is that when one reviews PFS with its clinical features and laboratory results, it becomes plain that this is an organic illness in which muscle metabolism is severely affected".

Human Enteroviral Infection EG Dowsett *J Hosp Inf 1988:11:103-115*

"Enteroviral syndromes range from trivial to severe and many are unrecognised or underinvestigated"

"Myalgic encephalomyelitis has been the cause of more than 50 epidemics….serious (neurological) sequelae are common….enteroviral infections in humans, as in animals, may be persistent"
"The main features (of ME) are prolonged fatigue following muscular exercise, an extended relapsing course which, unlike other postviral fatigue, lasts for months or years"

"An association with neurological, cardiac and other characteristic enteroviral complications (including) pancreatitis has long been recognised as part of severe generalised enteroviral infection".

Postviral fatigue syndrome: persistence of enterovirus RNA in muscle and elevated creatine kinase LC Archard, NE Bowles et al *JRSM 1988:81:325-331*

"These data show that enterovirus RNA is present in skeletal muscle of some patients with postviral fatigue syndrome up to 20 years after onset of disease and suggest that persistent viral infection has an aetiological role"

"These results provide further evidence that Coxsackie B virus plays a major role in ME, either directly or by triggering immunological responses which result in abnormal muscle metabolism".

Transmissible disease and psychiatry RP Yonge *JRSM 1988:81:322-325*

"This was the first time that it was possible to show unequivocally that there was an organic basis for the fatigue experienced by a patient diagnosed as having postviral syndrome"

"Nuclear magnetic resonance (imaging) has shown a metabolic basis for the fatigue experienced by some patients diagnosed as suffering from postviral fatigue syndrome"

"We have shown that muscle fatigue and weakness for which there has previously been no explanation is indeed in the muscle rather than in the mind".

Allergy and the chronic fatigue syndrome Stephen E Straus et al *J Allergy Clin Immunol*
1988:81:791-795

"Many patients report inhalant, food or drug allergies….this article emphasizes our assessment of one of (the syndrome's) more common manifestations, allergy"

"Attempts to avoid all the allergens further isolate the victims of 'total allergy' "

"A variety of immunologic abnormalities can be detected in patients with the chronic fatigue syndrome, abnormalities that suggest that the immune system may participate in the pathogenesis of this disease"

"It is possible that individuals with a heightened reactivity to allergens also respond more vigorously to certain infectious antigens…..inherent hyper-responsiveness would be the initiation by certain infectious agents of a level and duration of lymphokines and interleukin release that would in themselves perpetuate the reactive symptoms of the syndrome"

"Among the features of this syndrome is a high prevalence of allergy that appears to be substantial".

1989

Immunological abnormalities in the chronic fatigue syndrome Andrew R Lloyd, Denis Wakeford, Clement R Broughton and John M Dwyer *Med J Australia 1989: 151:122-124*

"A concurrent immunological disturbance is likely to be associated with the persistence of viral antigen"

"The finding of significantly increased numbers of peripheral blood mononuclear cells that express class II histocompatibility antigens (HLA_DR) in our patients implies immunological activation of these cells"

"These cell-surface antigens may have been induced by interferons or other cytokines. Once activated, these cells may continue to produce the cytokines which may mediate the symptoms of CFS".

Myalgic encephalomyelitis: postviral fatigue syndrome and the heart Norman Grist *BMJ 1989:299:1219*

"…similar immunological and metabolic disturbances in myalgic encephalomyelitis may also result from chronic infection, usually with enteroviruses, providing the organic basis of the postviral fatigue syndrome"

"This condition is characterised by severe fatiguability and recuperation through rest. The myocardium, however, cannot rest --- except terminally".

Postviral fatigue syndrome DO Ho-Yen *British Journal of Hospital Medicine 1989: 42:250*

"I believe that postviral fatigue syndrome is a distinct entity with a precise definition….in only a few patients is there confusion with psychiatric illness"

"As I understand the article *(referring to an article by Wessely),* graded exercise has been suggested but has **not** 'led to improvement in patients'. This article's *(ie. Wessely's)* suggestion of exercise until symptoms cease is the reason why a patient may be hospitalised".

1990

The diagnosis of postviral syndrome DJD Perrins *JRSM 1990:83:413*

"The clinical pattern of myalgic encephalomyelitis has much in common with multiple sclerosis".

The chronic fatigue syndrome: a return to common sense AM Denman
Postgraduate Medical Journal 1990:66:499-501

"It is salutary to reflect how many sufferers from infectious mononucleosis (glandular fever) may in the past have been maligned for their allegedly 'functional' illness before appropriate laboratory tests became available….similar considerations apply to chronic fatigue following enteroviral infection, particularly by…Coxsaclie B virus"

"In some patients, muscle pain and easy fatiguability may be so prominent as to suggest a separate diagnostic category 'myalgic encephalomyelitis'. This is also a point of practical importance if a form of the syndrome existed in which active physical rehabilitation were contra-indicated"

"Progress will only be achieved if the different categories of chronic fatigue are dissected with scientific objectivity and therapeutic reason".

Patient management of the postviral fatigue syndrome DO Ho-Yen *JRCGP 1990: 40:37-39*

"The subgroup of patients with immunological abnormalities may have a prolonged illness"

"…it has been suggested that a new approach to the treatment of patients with postviral fatigue syndrome would be the adoption of a cognitive behavioural model (Wessely S, David A, Butler S, Chalder T: Management of chronic (postviral) fatigue syndrome. *JRCGP 1989:39:26-29*). Those who are chronically ill have recognised the folly of the approach and, far from being maladaptive, their behaviour shows that they have insight into their illness".

Objective measurement of personality variables in epidemic neuromyasthenis patients
A.Sricklin et al *South African Medical Journal 1990:77:31-34*

"Too often only one aspect of the illness is treated….with little attention to other symptoms".

The psychiatric status of patients with the chronic fatigue syndrome Ian Hickie et al
Br J Psychiat 1990:156:534-540

"We conclude that psychological disturbance is likely to be a consequence of rather than an antecedent risk factor to the syndrome. Our results suggest that patients are no more psychologically disturbed before the onset of their illness than members of the general population"

"There is no evidence from our well-defined sample to support the hypothesis that CFS is a somatic presentation of an underlying psychological disorder. In particular, there is no evidence that CFS is a variant or expression of a depressive disorder".

Myalgic encephalomyelitis: an alternative theory CWM Wilson *JRSM 1990:83:481-483*

"In his discussion paper on myalgic encephalomyelitis (April 1989 JRSM), Wessely suggested that a new term should be used to describe the observed symptoms….In his definition of CFS, he did not refer to any of the somatic symptoms which are always present"

"Evidence of biochemical and neurological changes have been reported in the brain…. These symptoms are resistant to tranquillisers and antidepressant therapy in ME. Indeed, patients are often allergically sensitive to these drugs"

"The identification of viral antibodies in the tissues confirms the existence of a previous viral challenge".

CD8 Deficiency in patients with muscle fatigue following suspected enteroviral infection (myalgia encephalitica) JR Hobbs, JA Mowbray, JE Monro et al *In: Protides of the Biological Fluids 1990:36:391-398*

"Postviral states… have been shown to be associated with acquired (secondary) T-cell deficiencies, particularly with CD8 dysfunction, and even immune paresis"

"It is also clear that the acquisition of T-cell deficiency, particularly the CD8 subset, can itself impair immune regulation and predispose to atopy not previously experienced by the patient"
"It is known that psychological disturbance can influence immunity. We, ourselves, have undertaken extensive T-cell subset measurements in normal subjects subjected to psychological stress, and would point out that in none of these did we see CD8 levels as low as in some 40% of our ME patients"

"It seems unlikely that the severe CD8 deficiency found…could be due to psychological disturbance".

Immunologic Abnormalities in Chronic Fatigue Syndrome Nancy Klimas et al

J Clin Microbiol 1990:28:6:1403-1410

"The most consistent immunological abnormality detected among these patients, when compared with normal controls, was low natural killer (NK) cell cytotoxicity"

""Lymphocyte phenotypic marker analysis of peripheral blood lymphocytes showed that there were significant differences between patients with CFS and controls"

"The pattern of immune marker abnormalities observed was compatible with a chronic viral reactivation syndrome"

"Depression of cell-mediated immunity was noted in our study population, with over 80%
of patients having values below the normal mean"

"The values obtained were closely similar to those we observed in a group of human immunodeficiency virus type I-seropositive (HIV) intravenous drug users"

"Result from the present study indicate that there is an elevation in activated T-cells.
A strikingly similar elevation in CD2+ CDw26+ cells has been reported in patients with multiple sclerosis"

"Functionally, the CD45RA+ CD4 cells, also termed Tinf, for inflammatory CD4 cells, can transfer delayed-type hypersensitivity"

"Selective depletion of CD4+ CD45RA+ cells was noted during the active phases of multiple sclerosis, but not in patients in remission or with inactive multiple sclerosis or other neurological diseases. Deficiencies quantatively similar to those observed in patients with CFS were also reported in patients with other autoimmune diseases"

"The results of the present study suggest that CFS is a form of acquired immunodeficiency".

<u>Persistence of enteroviral RNA in chronic fatigue syndrome is associated with the abnormal production of equal amounts of positive and negative strands of enteroviral RNA</u> L Cunningham, NE Bowles, RJM Lane, V Dubowitz and LC Archard
J Gen Virol 1990:71:1399-1402

"This suggests that enteroviral persistence in muscle is due to a defect in control of viral RNA sythesis"

"These data are the first demonstration of persistence of defective virus in clinical samples from patients with CFS".

Myalgic encephalomyelitis --- a persistent enteroviral infection? EG Dowsett, AM Ramsay, RA McCartney, EJ Bell *Postgraduate Medical Journal 1990:66:526-530*

"Myalgic encephalomyelitis is a common disability but frequently misinterpreted"

"This illness is distinguished from a variety of other post-viral states by a unique clinical and epidemiological pattern of characteristic enteroviral infection"

"Advice to avoid over-exertion is mandatory"

"In our opinion, two major errors are responsible for the present confusion surrounding the case definition, aetiology and diagnosis of ME. First, there has been a failure to distinguish the syndrome from postviral debility following Epstein Barr mononucleosis, influenza and other common fevers. Second, there has been a failure to recognise the unique epidemiological pattern of ME".

1991

Chronic fatigue syndrome and depression Ian Hickie et al *Lancet 1991: (April 13):337*

"Kendell seeks to draw together similarities between CFS and depression but ignores important difference. Patients with typical depression are characterised by clinical features such as anhedonia, weight loss, suicidal ideation, psychomotor retardation or agitation
that are notably absent in CFS"

"Patients with CFS lack many essential characteristics of patients with primary depression; their symptoms more closely resemble those seen with depression complicating primary medical disorders".

Chronic fatigue syndrome: clinical condition associated with immune activation
Alan L Landay, Carol Jessop, Evelyne Lennette, Jay A Levy *Lancet 1991: (21 September):338:707-712*

"These findings further support the notion that CFS involves immune disorders due most likely to an infectious agent"

"…depression developed in many patents after two years of illness"

Group A consisted of 67 patients whose illness was so severe that they had less than 25% of their normal daily activity and also had multiple symptoms"

"Three cell surface markers gave noteworthy results….these data point to a high probability (90%) of having active CFS if an individual has two or more of the CD8 cell subset alterations"

"Evaluation of CD8 cell subsets in control subjects with a diagnosis of depression showed no significant differences compared with healthy controls"

"The immune disorder in CFS does not seem to reflect depression".

Mitochondrial abnormalities in the post-viral fatigue syndrome WMH Behan et al
Acta Neuropathol 1991:83:61-65

"The findings described here provide the first evidence that PFS may be due to a mitochondrial disorder precipitated by a virus infection"

"The pleomorphism of the mitochondria in the patients' muscle biopsies was in clear contrast to the findings in the normal control biopsies"

"Diffuse or focal atrophy of type II fibres has been reported, and this does indicate muscle damage and not just muscle disuse".

Evidence for Impaired Activation of the Hypothalamic Pituitary Adrenal Axis in Patients with Chronic Fatigue Syndrome Mark A Demitrack, Stephen E Straus et al
J Clin Endocrinology & Metabolism 1991:73:1224-1234

"Several lines of evidence suggest that the various components of the hypothalamic pituitary adrenal axis (the HPA axis) merit further study in these patients, for instance, debilitating fatigue, and abrupt onset precipitated by a stressor, arthralgias, myalgias, post-exertional fatigue, exacerbation of allergic responses and disturbances of mood and sleep are all characteristic of glucocorticoid insufficiency"

" a deficiency of CRH (cortico-releasing hormone) could theoretically contribute to the lethargy and fatigue that are the cardinal symptoms of CFS"

"Identification of psychological illness by standard diagnostic criteria includes many symptoms that are an inherent part of the definition of CFS"

Biopsychosocial aspects of Chronic Fatigue Syndrome JDL Yeomans, SP Conway
J Inf 1991:23:263-269

"CFS is associated with physical, psychological and social distress. The illness cannot be defined using just one of these dimensions. Such a unilateral approach has resulted in unnecessary controversy over the nature of the 'real' core of CFS"

"Psychiatric case definition is central to a psychiatrist's work and deserves careful attention in discussions of CFS with medical colleagues"

"It was hoped (that our present study) would avoid selection biases favouring the presence of psychiatric illness as might occur with selection by specialised fatigue clinics"

"A single item on the HAD depression scale refers to 'feeling slowed down'. Not surprisingly, this was cited by all patients. When this single item was removed from analysis, no patient retained a rating of depression. This emphasised the importance of possible false positive diagnosis of depression on the basis of somatic symptoms"

"Wessely and Powell (JNNP 1989:52:940948) found the total psychiatric morbidity in CFS was 72% ---other studies have found it to be 21%. (Our) study finds a variable prevalence depending on the criteria used. This emphasised the ease with which psychiatric rating scales may lead to false positive diagnoses in patients with physical symptoms"

"It is possible that studies of CFS have had a tendency to over-estimate the prevalence of depression"

"The absence of (biological markers) has been interpreted as support for a psychogenic aetiology for CFS. It is important to diagnose such syndromes correctly, and (our) study suggests that questionnaires alone may over-emphasise psychiatric syndromes"

"It is unnecessary and indeed unproductive to force patients into unsuitable diagnostic categories as a condition of treatment".

Postviral fatigue: current neurobiological perspective PGE Kennedy
In: Postviral Fatigue Syndrome. British Medical Bulletin 1991:47:4:809-814
Ed: PO Behan, DP Goldberg and JF Mowbray pub: Churchill Livingstone

"It is clear that there is now a widespread consensus that postviral fatigue syndrome (PVFS) is a definite disease entity….recent intense research has made it no longer acceptable to dismiss PVFS as non-organic"

"Molecular viral studies have proved to be extremely useful. They have confirmed the likely important role of enteroviral infections, particularly with Coxsackie B virus"

"The PVFS has now come of age as a definite organic entity".

The management of Post Viral fatigue Syndrome in General Practice David G Smith
ibid:265-279

"In the absence of any coherent move in Britain to develop criteria for the disease, the medical profession has had to fall back on the American Working Case definition of chronic fatigue syndrome (CFS), Holmes et al 1988, although this is not synonymous with ME".

Assessment and Diagnosis of ME in the Psychiatric Clinic Rachel Jenkins *ibid 241-246*

"Once one is familiar with the concept of post-viral fatigue syndrome, such patients are in practice not too difficult to differentiate from those with true psychiatric illnesses such as
depressive illnesses, anxiety, hypochondriasis or hysteria"

"The classic diurnal variation of mood in severe depressive illnesses is not seen: the patient with ME will relate their depression to the frustration felt at not being able to do the active things they enjoy doing"

"The depressed patient feels fatigued and will be unmotivated to exercise, but can do most activities if required and sustain them, including climbing a hillside, standing upright for two hours or carrying a heavy object. The sufferer with ME, on the other hand, cannot do more than a fraction of these activities"

"There are also subtle difference between the impairment of concentration in depression and that in ME; in ME, the impairment of concentration tends to be associated with the timing and severity of the fatigue"

"In addition, specific cognitive abnormalities are present in ME, including difficulty in marshalling material, difficulty in finding the correct words in a sentence, and in appropriate syntax; speech is sometimes slurred, and the patient appears more clumsy than usual. They tend to bump into doorways and furniture more frequently, may display old bruises, and may complain of a feeling of dysequilibrium

"The physical symptoms should be an aid to diagnosis, although they may be wrongly attributed to primary psychological illness unless care is taken in eliciting them"

"Under a regime of pushing beyond physical limits, severe relapses occur and physical limits decrease. This is the exact opposite of what happens in a depressed person who is otherwise physically well, where steady pushing beyond physical limits will extend those limits and increase physical fitness"

"People with this illness do not tolerate antidepressants well"

"Patients with postviral fatigue syndrome are often very scared and in considerable pain".

History of Chronic Fatigue Syndrome Stephen E Straus *In: Review of Infectious Diseases 1991:13: Suppl 1: S2-S7*

It is my goal to review briefly the history of CFS. In so doing, it becomes apparent that CFS is not of recent origin"

"Despite the broad divergence of opinion in the medical community, there is little doubt that classic allergy and atopy are inexplicably prevalent in CFS. In a recent study, a high proportion (50%) of patients were found to be reactive to a variety of inhalant or food allergens when innoculated epicutaneously in the classic manner"

"Because neurologic symptoms have dominated in certain of the case clusters (and even in some sporadic ones), the syndrome has been called benign myalgic encephalitis *(sic)*"

"Certainly patients with CFS differ immunologically from their healthy counterparts and it is this observation, more than any other today, that is evoked in support of the organic hypothesis of disease causation".

Defining the Chronic Fatigue Syndrome Gary P Holmes *ibid S53-S55*

"Preferably, patients with CFS who have such immune abnormalities might be considered
a subset of the larger group: ie. persons with CFS who have immune dysfunction".

Review of Laboratory Findings for Patients with Chronic Fatigue Syndrome
Dedra Buchwald and Anthony L Komaroff *ibid S12-S18*

"Those most consistently reported include depressed natural killer cell function and reduced numbers of natural killer cells; low levels of circulating immune complexes; low levels of autoantibodies, particularly antinuclear antibodies and antithyroid antibodies; altered levels of immunoglobulins; abnormalities in number and function of lymphocytes"

Chronic Fatigue Syndrome in Northern Nevada Sandra A Daugherty, Daniel Peterson, Sheila Bastien et al *ibid S39 - S44*

"The striking distortion of cognitive function along with the abnormal results of the MRI scans observed in these patients suggests a pathologic process in the brain"

"The pattern of focal and lateral impairments in these patients is more consistent with that of an atypical organic brain syndrome"

"This is not the pattern seen in depression, psychosis, anxiety or situational stress".

1992

Chronic Fatigue Syndrome N Phillips *Australia and New Zealand Journal of Psychiatry 1992:26:329-330*

" It is important for psychiatrists to familiarise themselves with the complexities of this syndrome and to be aware of the rapidly expanding body of new literature on this illness"

"Wessely's work on depression and CFS is methodologically flawed; (his patients) were not diagnosed using the full diagnostic criteria and therefore included many 'non-pure' CFS cases"

"Psychiatrists need to utilise such terminologies as 'the sick role' and 'abnormal illness behaviour' with great caution when discussing chronic illness. Not only will they alienate their medical colleagues, but, more importantly, the patients they are trying to help"

CFIDS Chronicle Special Bulletin Walter Gunn (Principal Investigator of CFS studies at the Centres for Disease Control (CDC), USA *February 1992*

"Our surveillance study does not support the notion that CFS is a psychiatric disease and, in fact, suggests that it has an organic basis".

Cell-mediated immunity in patents with chronic fatigue syndrome, healthy controls and patients with major depression A.Lloyd, I Hickie, J Dwyer et al *Clin Exp Immunol 1992:87:76-79*

"Evaluation of the psychiatric status of patients with CFS does not support the contention that CFS is simply a depressive quivalent"

"Although depression is common in patients with CFS, the disturbance in cell-mediated immunity in this disorder differs in prevalence and magnitude from those associated with major depression"

"It is likely therefore that this disorder is generated and maintained by an immunopathological process with the central nervous system".

A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpes Type 6 infection Dedra Buchwald, Paul Cheney, Robert Gallo *(co-discoverer of the HIV virus),* Anthony L Komaroff et al *Ann Intern Med 1992:116: 2:103-113*

"57% of patients were bed-ridden, shut in or unable to work"

"Immunologic (lymphcyte phenotying) studies revealed a significantly increased CD4 / CD8 ratio. Taken together, the controlled studies cited above and many others, seem to indicate an immune system chronically responding to a 'perceived' antigenic challenge"

"Neurologic symptoms, MRI findings, and lymphocyte phenotyping studies suggest that the patients may have been experiencing a chronic, immunologically- mediated inflammatory process of the central nervous system".

Possible up-regulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome AMO Bakeit, PO Behan, TG Dinan et al *BMJ 1992:304: 1010-1012*

""In the past few years evidence which shows the organic nature of this condition has accumulated"

"The results suggest upregulation of the hypothalamic 5-hydroxytryptamine (5-HT) receptors in patients with PVFS but not in those with primary depression"

"Most of these patients had objective evidence of muscle damage, as shown by mitochondrial changes and the persistence of enteroviral RNA sequenced in muscle"

Postviral fatigue syndrome Cosra DC, Brostoff J, Douli V, Ell PJ *BMJ 1992:304: 1567*

" (SPECT scans have demonstrated) significant deficits in brain perfusion, particularly in the hypothalamus and pons".

The postviral fatigue syndrome WRC Weir *Current Medical Literature (Royal Society of Medicine) 1992:6:1*

"In more acutely affected individuals the advice to 'exercise back to fitness' is a recipe for disaster".

Neuro-opthalmological manifestations of Chronic Fatigue Syndrome Alfredo A Sadun and Pravin U Dugel *In:* The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome *Ed:* Byron M Hyde, Jay Goldstein and Paul Levine
pub: The Nightingale Research Foundation, Ottawa, Canada 1992

"The neuro-opthalmological manifestations of CFS are myriad and common. Two thirds of the patients complained of blurred vision; one patient (complained of) binocular diplopia. The most obvious objective signs was nystagmus; it was even more astonishing that approximately one quarter of the patients had a primary nystagmus, since such nystagmus is always pathological".

1993

Biochemical and muscle studies in patients with acute onset postviral fatigue syndrome
VR Preedy et al *J Clin Pathol 1993:46:722-725*

"Patients with acute onset PVFS lose muscle protein synthesis potential, but not muscle bulk. Histopathology is consistent with these observations. These peturbations may contribute to the apparent feature of perceived muscle weakness associated with the persistent viral infection in the muscles themselves".

Persistence of enterovirus RNA in muscle biopsy samples suggest that some cases of chronic fatigue syndrome result from a previous, inflammatory viral myopathy
NE Bowles, LC Archard et al *Journal of Medicine 1993:24:2:145-160*

"The term PVFS has been widely misused to describe all form of chronic fatigue"

"Investigation with strand-specific riboprobes demonstrated that in each of the PFS cases found positive for virus RNA, enterovirus persisted in these non-inflammatory muscle biopsies as a replication defective mutant"

"Our data confirm that enterovirus infection of muscle is not a general feature of the population"

"This association of enterovirus infection is compatible with what is often considered an autoimmune disease"

"We propose that in PFS patients, a mutation affecting control of viral RNA synthesis occurs during the initial phase of active virus infection and allows persistence of replication defective virus which no longer attracts a cellular immune response".

1994

Summary and Perspective: Epidemiology of Chronic Fatigue Syndrome Paul H Levine
Clin Inf Dis 1994:18: (Suppl 1):S57-S60

"Epidemiologists play a number of roles in the study of diseases; the functions of these specialists include case definitions, descriptions of disease patterns, identification of risk

factors, and analysis of clinical trials. In the study of a complex illness such as CFS, for which no definitive diagnostic test exists, the most important aspect is case definition – all other areas of investigation depend on this standard for appropriate interpretation of results"

Most patients affected in a cluster of 'epidemic neuromyasthneia' do not fit the 1988 case definition of CFS"

"It has been noted for a number of years that a history of allergies appears to be an important risk factor for CFS"

"**The spectrum of illnesses associated with a dysregulated immune system must now include CFS**"

"The precipitating factors leading to CFS were also an important focus of this symposium.
In addition to a history of allergy, other factors such as **exposure to chemicals and noxious agents** were noted to be possible triggers"

"It is likely that host response, due to genetic predisposition, contributes to the development of CFS **as an outcome of the exposure".**

Association between HLA Class II Antigens and the Chronic Fatigue Immune Dysfunction Syndrome RH Keller, MA Fletcher, N Klimas et al *ibid S154-S159*

"The chronic fatigue immune dysfunction syndrome (CFIDS) is a major subgroup of the chronic fatigue syndrome (CFS). We and other investigators have reported a strong association between immune dysfunction and a serological viral reactivation pattern among patients in this group. This finding appeared similar to that for a variety of conditions such as chronic active hepatitis, juvenile rheumatoid arthritis and systemic lupus erythematosus (SLE or lupus), in which a definite association between a particular HLA-DR/DQ haplotype and increased disease frequency has been reported"

"It is possible that DR4 (relative risk for CFIDS 1.6) and DR5 (relative risk for CFIDS 1.8) are also associated with an increased risk of developing CFIDS"

"The data presented herein suggest that CFIDS, together with a variety of immune-mediated diseases, may share similar sequences of pathogenic mechanisms"

"It may be speculated that in a particular sub-population, a genetic predisposition may be triggered immunologically by any of a number of potential stimuli, resulting in a state of chronic immune dysequilibrium"

"This model could easily explain the recent findings with regard to acute viral infection, allergies or other mechanisms that are obscured by the process of chronic immune activation".

Decreased Natural Killer Cell Activity is Associated with Severity of Chronic Fatigue Immune Dysfunction Syndrome EJ Ojo-Amaize et al *ibid S157-S159*

"Our results confirm and extend previous reports that low NK cell cytotoxicity is a pronounced immunologic abnormality found in some patients with CFIDS"

"The fact that NK cell activity decreases with the increased severity and duration (of the disorder) suggests that measurement of NK cell function could be useful for stratification of patients and for monitoring the progression of CFIDS".

Closing Remarks of the Symposium Anthony L Komaroff and Nancy Klimas
ibid S166-167

"Few studies by psychiatrists are presented in this symposium. Many investigators who have argued that CFS is primarily a psychiatric disorder chose not to present their work".

Simultaneous Measurement of Antibodies to Eppstein Barr Virus, Human Herpes Virus 6, Herpes Simplex Virus Types 1 and 2, and 14 Enteroviruses in Chronic Fatigue Syndrome:
Is there evidence of Activation of a Nonspecific Polyclonal Immune Response?
FA Manian *Clin Inf Dis 1994:19:44-53*

"Of the 14 enteroviruses tested for, (only) those to Coxsackie B1 and B4 were present at significant titres in cases versus controls at a percentage significantly higher than that of controls".

1995

'Abnormal' Illness Behaviour in Chronic Fatigue Syndrome and Multiple Sclerosis
Peter Trigwell, Simon Hatcher *BMJ 1995:311:15-18*

"Those who see CFS as primarily a psychiatric disorder regard it as a variety of somatisation. The concept of somatisation overlaps with that of 'abnormal illness behaviour'. There is an explicit judgment to be made in concluding that a patient is exhibiting abnormal illness behaviour: it is that the doctor does not think that the patient's objective pathology entitles him to be placed in the sick role he expects"

"If CFS is a variety of somatisation, then we should expect to find evidence of abnormal illness behaviour with the syndrome"

"We wanted to confirm whether patients with CFS have abnormally high levels of disease conviction and if so, whether it is associated with other elements of abnormal illness behaviour or is, indeed, merely a corrollary of chronic disease"

"We draw two conclusions from our study. Firstly, the illness behaviour questionnaire seems to be unsatisfactory as a measure of abnormal illness behaviour in CFS. Secondly, we have confirmed that disease conviction is common in CFS"

"Score on illness behaviour questionnaires cannot be taken as evidence that CFS is a variety of abnormal illness behaviour because the same profile occurs in multiple sclerosis".

Exercise response and psychiatric disorder in chronic fatigue syndrome Russell JM Lane,
Leonard C Archard et al *BMJ 1995:311:544-545*

"In previous studies patients with the CFS showed exercise intolerance in incremental exercise tests, which seemed to be related to an increased perception of effort. We examined venous blood lactate responses to exercise at a work rate below the anaerobic threshold in relation to psychiatric disorder"

"Our results suggest that some patients with the CFS have impaired muscle metabolism that is not readily explained by physical inactivity or psychiatric disorder".

Brainstem perfusion in chronic fatigue syndrome DC Costa, C Tannock, J Brostoff
Quarterly Journal of Medicine 1995:88:767-773

"Patients with ME/CFS have a generalised reduction of brain perfusion, with a particular pattern of hypoperfusion of the brain stem".

Detection of Enterovirus-specific RNA in Serum: the Relationship to Chronic Fatigue
Geoffrey B Clemenst et al *J Med Virol 1995:45:156-161*

"In the study described here, enteroviral sequences were found in significantly more CF patients than in the teo comparison groups. The presence of the enteroviral sequences in a significant number of patients points to some role in CF"

"A variety of immunological disturbances have been reported for CF patients which may relate in some way to the enteroviral persistence"

"This study provides evidence for the involvement of enterovirusrs in just under half of the patients presenting with CF and it confirms and extends previous studies using muscle biopsies"

"We provide evidence for the presence of viral sequences in serum in over 40% of CF patients and also in some buffy coat cells and stool samples".

Pathophysiology of a Central Cause of Post Polio Fatigue Richard L Bruno et al
In: Ann NY Acad Sci 1995:753:257-275

"These relationships and recent empirical comparisons between post polio and chronic fatigue will be described"

"Beginning in Los Angeles in 1934 and continuing for more than 20 years, a dozen outbreaks occurred of a disease that was at first diagnosed as poliomyelitis, then as 'atypical' poliomyelitis and finally named myalgic encephalomyelitis (ME)"

"Most patients wre left with a marked exhaustion and fatiguability that were always made worse by exercise and emotional stress"

"A more direct association between the polio virus and ME was seen in 1948"

"More recent support for a relationship between poliovirus and ME came in 1989 when a dangerously rising titre to type III poliovirus was documented in a patient who did not have polio but who had been diagnosed with ME"

"A constellation of symptoms resembling ME was termed 'chronic fatigue syndrome' (CFS) --- like ME and post-polio fatigue, CFS is characterized by complaints of chronic fatigue and impaired concentration that are triggered or exacerbated by physical exertion and emotional stress"

"Hyperintense signal imaged along white matter tracts may have resulted from damage to the brain parenchyma by a local, tissue-toxic effect of the poliovirus"

"Notably, periventricular and deep white (but not grey) matter HS have been imaged in between 40 and 100% of CFS patients and have been suggested to represent either enlarged, fluid-filled spaces around arterioles, or demyelination"

"Neuroradiologic and neuroendocrine data have indicated damage to brain areas responsible for cortical activation and attention in polio survivors and others with chronic fatigue"

"Word-finding difficulties are reported by 82% of polio survivors with fatigue, and appear similar to word-finding problems reported by CFS patients".

1996

Prognosis in chronic fatigue syndrome: a prospective study on the natural course
JM Vercoulen et al *JNNP 1996:60:489-494*

"Comprehensive assessment of CFS entails measurement on all dimensions simultaneously"

"The finding that on three out of seven outcome measures these patients did not show improvement underlines the importance of multidimensional assessment in studies on prognosis"

"Psychological well-being (including depression) did not predict improvement in this study, although others (Wessely et al) have suggested that this factor plays a part in the perpetuation of complaints"

"Avoidance of physical activity is also thought to play a part in the perpetuation of complaints (Wessely et al) but the present study is not conclusive on this issue"

"The improvement rate in patients with a relatively long duration of complaints is small".

Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. Jan H M M Vercoulen, Caroline Swanink et al: *Lancet, 1996:347:858-861*

"Antidepressant therapy is commonly used (in CFS). However, there has been no randomised, placebo-controlled double-blind studies showing the effectiveness of antidepressant therapy in CFS. We have carried out such a study to assess the effect of fluoxetine *(Prozac)* in depressed and non-depressed CFS patients".

"There have been anecdotal reports that fluoxetine is poorly tolerated by patients with CFS. In our trial, 15% of fluoxetine-treated patients withdrew because of side effects, a higher withdrawal rate than in fluoxetine trials in depressed patients on the same regime".

"In our study, fluoxetine was no better than placebo in treating depression".

"Fluoxetine in a 20 mg daily dose does not have a beneficial effect on any characteristic of CFS".

"We conclude that prescription of 20mg fluoxetine in CFS is unwarranted, irrespective of whether depressive symptoms are present; it does not lead to improvement in any area of the patient's functioning".

Chronic Fatigue Syndrome: is total body potassium important? Burnet RB et al. *Medical Journal of Australia, 1996:164:6:384*

The authors found that total body potassium (TBP) was lower in patients with CFS and they suggest that abnormal potassium handling by muscle in the context of low overall body potassium may contribute to fatigue in CFS.

Lung function test findings in patients with chronic fatigue syndrome.
De Lorenzo et al. *Australia and New Zealand Journal of Medicine, 1996:26:4:563-564.*

The authors found that compared with controls, patients with CFS showed a significant reduction in all lung function parameters.

Abnormality of adrenal function in the patients with chronic fatigue syndrome.
Yamaguti K et al. *JCFS, 1996:2:2/3.* Abstract of presentation at the Proceedings of the First World Congress on CFS, Brussels, November 9-11,1995.

"The level of DHEA decreases in some patients and the level of DHEA - S decreases in most patients with CFS. These abnormalities found in CFS are quite different from those found in patients with mental and physical diseases reported previously".

Eosiniphil cationic protein serum levels and allergy in chronic fatigue syndrome.
Conti F et al. *Allergy: 1996:51:124-127*

"ECP serum levels were significantly higher in CFS patients than in controls. In CFS patients, the prevalence of radio-allergosorbent (RAST) positive responses to one or more allergens was 77%, while no control showed positive RAST".

Chronic Fatigue Syndrome: evaluation of a 30-criteria score and correlation with immune activation. Hilgers A and Frank J. *Journal of Chronic Fatigue Syndrome,1996:2:4:35-47.*

The aim of this study was to develop a score to evaluate the severity of CFS and to correlate the degree of severity with parameters of immune activation; five hundred and five patients were studied using a 45-criteria score and basic laboratory programmes, together with immunological profiles. In most of the patients, further tests of complement system, immune activation markers, hormones and viral serology were evaluated.

385 patients fulfilling the 1994 CDC criteria showed significant differences to healthy controls in 40 of the 45 symptoms assessed. Thirteen symptoms corresponding to CDC criteria were all significant, but 17 further significant criteria were added to improve precision:

respiratory infections; palpitations; dizziness; dyspepsia; dryness of mouth / eyes; allergies; nausea; paraesthesia; loss of hair; skin alterations; eczema; dys-coordination; chest pain; personality changes; general infections; urogenital infections; twitches.

A correlation between the 30-criteria score and immunological parameters could be evaluated in 472 of the 505 patients.

Significant positive correlation was found in numbers of CD8+ T lymphocytes, HLA DR+ lymphocytes, gamma globulins, 1gM, lgG, and for the numbers of types of autoantibodies (mainly ANA, ACA, antithyroid and antiparietal cell antibodies).

Significant negative correlation was found in albumin-globulin ratio, eosinophils and lgE.

Most of these parameters also correlated with one another.

"In increasingly larger groups of patients with CFS and related constellations we often see clinical signs and longer anamnesis of other symptoms beside the classical criteria of CFS, especially a high prevalence of local and general infections and hints to prolonged inflammation processes…A reduced or unstable immune control can lead to a chronic neuro-immune activation state and autoimmune disorders. Hypersensitivity symptoms of the patients might not be mediated by classical allergies alone but also result from a type IV hypersensitivity".

The neuroendocrinology of chronic fatigue syndrome. Scott LV, Dinan TG.
JCFS: 1996:2:4:49-59

The authors note that there is an increasing volume of evidence to support the view that patients with CFS have unique neuroendocrinology patterns.

Central to this endocrine dysfunction is altered hypothalamic-pituitary-adrenal axis (HPA) activity.

The cardinal findings include attenuated adrenocorticotrophic hormone (ACTH) responses to corticotrophin-releasing hormone (CRH) and low 24 hour urinary cortisol. These are compatible with a mild central adrenal insufficiency.

Adrenal steroids have widespread impact in the brain, and of particular importance is their dense concentration on serotonergic and noradrenergic neurotransmitter pathways.

The authors propose that the disruption of the HPA axis (which may be triggered by a number of stressors) may represent a primary phenomenon, and that neurotransmitter abnormalities (serotonin and noradrenalin) are in fact secondarily heralded by prolonged HPA dysregulation.

Evidence that abnormalities of central neurohormonal systems are key to understanding Fibromyalgia and Chronic Fatigue Syndrome. Leslie J.Crofford and Mark A.Demitrack.
Rheum Dis Clin North America:1996:22:2:267-284

The concept that disorders such as fibromyalgia (FM) and chronic fatigue syndrome (CFS) are associated with subtle and undetectable disturbances in the central nervous system was introduced in 1869 by Beard. Great strides have been made in recent years towards defining neurochemical abnormalities in FM and CFS, and both FM and CFS fall into the spectrum of what might be termed *stress-related illnesses* by virtue of the clinical observation that the onset of both is coincident with physical or emotional stress. The article focuses on abnormalities of the HPA axis and sympathetic nervous system (SNS), ie. the major stress response systems, and the authors point out that it is important to keep in mind that activity of stress response systems is determined by genetic and environmental factors.

The authors present data which supports the view that FM and CFS could represent different forms of insufficient stimulation of the HPA axis, with both syndromes expressing low hypothalamic CRH but with FM being characterised by *increased* exposure of the corticotrophs to AVP, while CFS patients have *decreased* AVP levels. Patients with a longer duration of disease tend to have more severe basal abnormalities in cortisol levels.

When estrogenic stimulation diminishes, relative hypo-function of the HPA axis could follow, contributing to the development or maintenance of FM / CFS.

Further research into the nature of the neurohormonal peturbations in FM and CFS may elucidate treatment strategies for these disorders.

Neuroimmune mechanisms in health and disease. Part 2: Disease. Anisman H. et al.
Can Med Assoc.J: 1996:155(8) 1075-1082

In the second part of their article on the emerging field of neuroimmunology, the authors present an overview of the role of neuroimmune mechanisms in defence against infectious disease and in immune disorders. Profound neuroendocrine and metabolic changes take place: acute phase proteins are produced in the liver; bone marrow function and the metabolic activity of leukocytes are greatly increased, and specific immune reactivity is suppressed. Defects in regulatory processes (which are fundamental to immune disorders and inflammatory diseases) may lie in the immune system, the neurendocrine system or both.

Defects in the HPA axis have been observed in autoimmune disease, chronic inflammatory disease, chronic fatigue syndrome and fibromyalgia.

Defective neural regulation of inflammation is likely to play a pathogenic role in allergy and in gastrointestinal inflammatory disease.

A better understanding of neuroimmunoregulation holds the promise of new approaches to the treatment of immune and inflammatory disease with the use of hormones,

neurotransmitters and neuropeptides and drugs which modulate these newly recognised immune regulators.

Prevalence of irritable bowel syndrome in chronic fatigue. Gomborone JE et al. *JRCP Lond 1996:30:6:512-513*

The purpose of this study was to determine the prevalence of irritable bowel syndrome in chronic fatigue sufferers.

A questionnaire about bowel symptoms was sent to 4,000 members of Action for ME self help group, and was returned by 1,797 (45%).

The people with chronic fatigue reported more bowel symptoms including the Manning criteria than the general population.

Seventy three per cent qualified for the diagnosis of IBS, which greatly exceeds estimates of lBS prevalence of up to 22% in the general population.
The researchers suggest that CFS and lBS may overlap in pathogenesis.

Decreased vagal power during treadmill walking in patients with chronic fatigue syndrome. Cordero DL, Natelson BH et al. *Clin Auton Res: 1996:6:(6):329-333*

The purpose of this study was to determine if patients with CFS have less vagal power during walking and during rest periods following walking.

Patients had significantly less vagal power than the control subjects, despite there being no significant group-wise differences in mean heart rate, tidal volume, minute volume, respiratory rate, oxygen consumption or total spectrum power.

Notably, patients with CFS had a significant decline in resting vagal power after periods of walking.

These results suggest a subtle abnormality in vagal activity to the heart in patients with chronic fatigue syndrome.

Autoantibodies to Nuclear Envelope Antigens in Chronic Fatigue Syndrome
K.Konstantinov, D.Buchwald, J.Jones et al. *J.Clin Invest 1996:98:8:1888-1896*

The authors identified and partially characterised the autoantibodies in sera of 60 patients with CFS. The autoantibodies were of the lgG isotype.

The occurrence of autoantibodies to a conserved intracellular protein like lamin BI provides new laboratory evidence for an autoimmune component in CFS.

The immunological abnormalities described are in accordance with a growing body of evidence suggesting chronic, low-level activation of the immune system in CFS.

The authors found that 52% of patients with CFS develop autoantibodies to components of the nuclear envelope (NE), mainly nuclear lamins. Their findings suggest that in addition to the other disturbances of the immune system, humoral autoimmunity against polypeptides of the NE is a prominent immune derangement in CFS.

67% of CFS patients were positive for NE reactivity, compared with 10% of normal subjects in control groups I and II. In addition, none of the patients with chronic depression or atopy showed reactivity to NE proteins.

These results confirm that the NE reactivity of some CFS sera is against lamin B. Autoantibodies to NE proteins are relatively infrequent in routine ANA serology, and most of these fall into the broad category of an unusual connective tissue disease subset characterised by brain or skin vasculitis.
The authors state that future work should be directed at a better understanding of the autoimmune response of CFS patients to other NE proteins.

Randomized, double-blind, controlled placebo-phase in trial of low dose phenelzine in the chronic fatigue syndrome Benjamin H.Natelson et al. *Psychopharmacology 1996:124: 226-230*

The authors investigated the possibility that CFS was a disorder of reduced central sympathetic drive; their study allowed the authors to evaluate patients for a placebo effect: no evidence for this was found, suggesting that CFS is not an illness due to patients being overly suggestible, and negating the proposal by some investigators that CFS is not a disease at all but simply a form of aberrant illness behaviour related to the suggestibility of the patient.

The authors conclude that their results are certainly not consistent with what might be expected in suggestible patients with psychogenic illness.

The authors state that “no clear effect of any commercially available treatment has ever been demonstrated in this devastating illness”.

1997

Evidence for enteroviral persistence in humans Daniel N.Galbraith, Carron Nairn and Geoffrey B.Clements. *Journal of General Virology 1997: 78:307-312*

The authors present for the first time evidence for enteroviral persistence in humans based on sequence comparison of serial PCR products from the 5' non-translated region (NTR).

A group of CFS patients was being followed prospectively, and showed closely related enteroviral sequences containing a unique shared pattern detectable in sera of individual patients for up to 24 months, providing good evidence for viral persistence.

The sequences from the CFS patients form a group demonstrating a close genetic relationship with each other, and fall into a subgroup that is related to Coxsackie B viruses.

The authors point out that co-existence of populations of different enteroviral sequences has been shown in poliovirus where reversion of attenuated vaccine strains to a neurotropic type can occur in an individual.

Biochemical Evidence for a Novel Low Molecular Weight 2-5A-Dependent RNase L in Chronic Fatigue Syndrome Robert J.Suhadolnik, Daniel L.Peterson, Paul R.Cheney, Kenny de Meirleir et al *Journal of Interferon and Cytokine Research 1997:17:377-385*

Previous studies from this laboratory have demonstrated a statistically significant dysregulation in several key components of the 2' 5'A synthetase / RNase L and PKR antiviral pathways in CFS. The 2-5A synthetase *I* RNase L pathway is part of the antiviral defence mechanism in mammalian cells.

An accumulating body of evidence suggests that CFS is associated with dysregulation of both humoral and cellular immunity, including mitogen response, reactivation of viruses, abnormal cytokine production, diminished natural killer (NK) cell function and changes in intermediary metabolites.

Marked and striking differences have been observed in the molecular mass and RNase L enzyme activity of 2-5A binding proteins in extracts of PBMC from individuals with CFS compared with healthy controls.

The authors present biochemical evidence for an RNase L enzyme dysfunction in CFS, in particular for an upregulated RNase L activity associated with CFS.

The biochemical and immunological data presented in this paper have identified a potential subgroup of individuals with CFS with an RNase L enzyme dysfunction that is more profound than previously observed in CFS, and which the authors believe is related to the severity of CFS symptoms.

Elevation of Bioactive Transforming Growth Factor-ß in Serum from Patients with Chronic Fatigue Syndrome Adrienne L.Bennett, Dedra Buchwald, Anthony L.Komaroff et al. *Journal of Clinical Immunology: 1997:17:2:160-166*

The authors provide evidence that patients with CFS had significantly higher levels of bioactive TGF-ß levels compared to the healthy controls, to patients with major depression, patients with SLE, patients with relapsing/remitting multiple sclerosis and patients with CP MS, ie. that in patients with CFS, the levels were significantly higher compared to patients with various diseases known to be associated with immunologic abnormalities and *I* or pathologic fatigue.

The authors state that perhaps of greatest relevance to CFS are the effects of TGB-β on cells of the immune and central nervous systems, and the evidence that it may play a role in autoimmune and inflammatory disease.

Elevated apoptotic cell population in patients with chronic fatigue syndrome: the pivotal role of protein kinase RNA A.Vojdani, CW Lapp et al. *Journal of Internal Medicine 1997:242:465-478*

The authors state that a prominent feature of CFS is a disordered immune system and recent evidence indicates that induction of apoptosis *(programmed cell death)* might be mediated in a dysregulated immune system by the upregulation of growth inhibitory cytokines.

The authors' results are in agreement with previous reports on abnormal cytokine production in CFS patients.

Quantatitive analysis of apoptotic cell population in CFS patients has shown a statistically significant and marked increase compared with healthy controls. Such an abnormality in cell cycle progression is an indication of abnormal mitotic cell division.

Activation of PKR can result in inhibition of protein synthesis and induction of apoptosis, and activation of the PKR pathway could result from a dysregulated immune system or from chronic viral infection.

Blunted serotonin-mediated activation of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome Timothy G.Dinan, Tahir Majeed, Peter Behan et al *Psychoneuroendocrinology 1997:22:4:261-267*

The authors state that CFS is a clinically defined syndrome in which serotonergic activation of the HPA axis is defective, with the release of ACTH (but not cortisol) in response to ipsapirone challenge being significantly blunted, and that patients with CFS

show disturbances of HPA function which differ markedly from those seen in melancholic depression.

The authors note that an increase in peripheral turnover of the major metabolite of 5HT might explain the heightened allergic responsiveness, as well as the musculoskeletal pain seen in CFS patients.

Politics. Science, and the Emergence of a New Disease Leonard A.Jason, Karen M.Jordan et al. *American Psychologist:1997:52:9:973-983*

This paper states that many physicians minimised the seriousness of CFS and interpreted the symptoms as being equivalent to a psychiatric disorder; the authors state that these attitudes have had negative consequences for the treatment of CFS.

They point out that use of the original case definition of CFS and the type and scoring of psychiatric tests appear to have produced erroneous estimates of the extent of CFS comorbidity with psychiatric disorders.

The authors specifically mention the work of Wessely, pointing out that he was "influential", and also pointing out that Wessely's findings have led some to conclude that CFS is solely a psychiatric disorder.

The authors comment on "unfortunate biases" having been introduced, and they point out that the DIS (a structured psychiatric instrument designed for use in community surveys) has frequently been used to assess psychiatric comorbidity in CFS, when that instrument was not designed for use with *medically* ill populations.

The authors point out that high or low psychiatric rates in CFS samples may relate to whether symptoms are attributed by physicians to psychiatric or non-psychiatric cause.

The authors consider methodological problems with the "broadened" case definition (as advocated by Wessely et al to include all cases of unexplained "fatigue" lasting for at least one month), and point out that by broadening the CFS definition, it is important to ensure that those patients with solely a psychiatric disorder are not erroneously included within the CFS rubric, as to do so could seriously complicate the interpretation of epidemiological and treatment studies.

Professor Jason points out that some CFS investigators would not see this as a confounding problem because they believe that high rates of psychiatric comorbidity indicate that CFS is mainly a psychiatric disorder.

The authors urge caution with graded exercise regimes in CFS, saying that for those CFS individuals who do not have psychologically mediated reductions in activity, such a directed approach would be inappropriate and could even be counterproductive.

The authors point out that differences observed by investigators (named as Sharpe et al, a UK psychiatrist and close collaborator of Wessely) could well be due to Sharpe's focus on illness beliefs, so Sharpe's sample of CFS patients might have been less impaired than a severely ill group.

The authors re-iterate that biases in the scoring and selection of psychiatric tests contributed to high levels of psychiatric comorbidity in CFS claimed by this group of psychiatrists, and that these findings were possibly due to the psychiatrists' belief that CFS was predominantly a psychiatric rather than a medical disorder, and that the findings were influenced by "flawed epidemiological research".

The papers states "Other investigators, such as Wessely et al, believe that CFS represents an arbitrarily defined end point and that there are no clear cutoff points separating those with severe fatigue from CFS".

"Psychiatrists and physicians have also regarded fatigue as one of the least important of presenting symptoms (Lewis and Wessely, *1992)*. These biases have been filtered to the media, which has portrayed CFS in simplistic and stereotypic ways".

The authors comment on the disregard of the *severity* of CFS symptoms; they conclude by commenting "We believe that it is crucial for CFS research to move beyond fuzzy recapitulations of the neurasthenia concept and clearly delineate precise criteria for diagnosing pure CFS".

Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease John de Luca, Benjamin H.Natelson et al
JNNP 1997:62:151-155

The authors conclude that impaired cognition in CFS cannot be explained solely by the presence of a psychiatric condition and is contrary to expectations based on a model of "depression - induced" cognitive impairment in CFS.

"The results of the present study suggest that at least in a subgroup of patients, CFS is not simply a manifestation of a primary psychiatric disorder".

Neuroendocrine correlates of chronic fatigue syndrome: a brief review Mark A.Demitrack. *J Psychiat* Res *1997:31:1:69-82*

The author begins his review by stating "Over time, it has not escaped the view of clinical authors that CFS and its historical antecedents shares many characteristics with endocrine disease states.. ..contemporary clinical research efforts have clearly documented that neuroendocrine disturbances are evident in patients with CFS".

"In almost all studies, at least 25% of subjects show no evidence, either past or current, for formally diagnosable psychiatric illness".

"Indeed, the accumulating body of evidence is contributing to a view of CFS as a disorder which is, in part, characterised by a novel dysregulation of the stress response".

The author surveys the published literature of neuroendocrine abnormalities in patients with CFS; he provides confirmatory support for an impairment of the HPA axis (consistent with the view that adrenocortical function is impaired); he notes the overall observation of reduced adrenocortical activation is a common feature to both fibromyalgia and chronic fatigue syndrome; he underlines the role of stress in the onset and course of CFS, and provides concluding remarks on the implications of this work.

Epidemiological Advances in Chronic Fatigue Syndrome. Paul H.Levine

J psychiat Res 1997:31:1:7-18

The author begins by noting that "Epidemiologic studies of CFS have been hampered by the absence of a specific diagnostic test.. ..working case definitions have not always been utilized precisely by various investigators.. ..the separation of those patients with and without pre-existing depression and other psychologic diagnoses that are not exclusive to CFS continues to be of major importance".

The author comments specifically on the fact that all physical findings were dropped from the CDC 1994 case definition of CFS *(note that UK psychiatrist Michael Sharpe is a named co-author of this revised definition and that Wessely is listed as being a member of the International Chronic Fatigue Syndrome Study Group, who produced the CDC 1994 definition)*

The author states "Not surprisingly, the differences among these and earlier studies persist due to the different populations evaluated".

This author (as others) notes that "The effect of stress on the neuroendocrine and immune function is being increasingly well characterised".

He states "The data suggest a poorer prognosis in those with more severe debilitation for a prolonged period of time".

This author is another to comments specifically that "The importance of the definition of subgroups is apparent. The heterogeneity of the disorder clearly highlights their existence".

The author points out that "The most important risk factors for CFS continue to be gender and a recent history of severe stress".

Precipitating Factors for the Chronic Fatigue Syndrome. Irving E.Salit.
J psychiat Res 1997:31:1:59-65

This author also points out that "Stressful events were very common in the year preceding the onset of CFS". He concludes by stating "Even more compelling is the evidence that CFS can and does occur after physically traumatic events such as motor vehicle accidents".

The Quality of Life of Persons with Chronic Fatigue Syndrome JS Anderson and CE Ferrans. *The Journal of Nervous and Mental Disease l997:185:5:359-367*

The purpose of this study was to explore the quality of life (QOL) of persons with CFS. Over all scores on the quality of life index, people with CFS were significantly lower than for other chronic illness groups.

The authors conclude that “The findings suggest that quality of life is particularly and uniquely disrupted in CFS”.

The authors note that there has been little research into this aspect, and their study revealed that 90% of their sample group experienced frequent feelings of isolation, alienation and inadequacy due to CFS.

The warn that what may be considered a disability for one person may be merely a nuisance for another, and they point out that the QLI is one of the few available instruments which takes account of this phenomenon, and that the reliability and consistency of the QLI is well established.

All participants stated that CFS had had a profound impact on every aspect of their lives in ways they had never imagined possible.

All participants related profound and multiple losses, including the loss of jobs, relationships, financial security, future plans, daily routines, hobbies, stamina and spontaneity, and even their sense of self because of CFS. Activity was reduced to basic survival needs in some subjects.

These profound losses significantly affected the participants’ mental health and outlook for the future.

Participants had difficulty in describing their illness because of the marked variability in symptoms. Symptoms were reported to be multiple, diverse, variable and pervasive. Participants reported that symptom variability tended to impede diagnosis and credibility and made it difficult for them to adjust and cope with the illness. Symptom variability also made it impossible for those with CFS to predict their level of functioning, which interfered with efforts to plan activities. For this reason, symptom variability was regarded as an especially frustrating aspect of CFS, and the uncertainty was one of the most difficult aspects of CFS to deal with.

Patients reported that they were exhausted and could not function, and that “it never goes away”.

All participants (100%) felt that CFS had devastated social relationships and activities: “Friends of 15 years stopped returning my calls and quietly disappeared”. A third reported that they had lost most, if not all, of their previous friendships; 18% currently had no friends whatsoever. Several participants reported that they had no family.

The authors conclude that the extent of the losses experienced in CFS was devastating, both in number and in intensity.
Participants described a sense of hopelessness that was integral to the illness due to symptom variability, length of illness and repeated relapses. Over time, those who were initially optimistic became emotionally exhausted.

Patients were particularly concerned about their long-term financial needs.

The authors note that such fatigued patients may lack the energy to seek out social support, and they may lack the energy to maintain existing relationships.

The authors found that the impact of CFS on patients' life was so total and so devastating that participants had difficulty in accepting their illness and its consequences.

The authors conclude by stating "CFS is a poorly understood and often trivialized illness, which in reality causes marked disruption and devastation".

A 56 year old woman with Chronic Fatigue Syndrome: Clinical Crossroads: Conference Report. Anthony L Komaroff. *JAMA, 1997: 278:14:1179 -1185*

(This conference took place at the Medicine Grand Rounds of the Beth Israel Deaconess Medical Center, West Campus, Boston, Mass. on June 11th 1997. Dr Komaroff is Professor of Medicine, Division of General Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, Mass. He is a world acclaimed expert on ME/CFS)

Dr Komaroff told the Conference that two themes emerge: (I) the enormous frustration of suffering from an illness that is poorly understood and (ii) the loss of legitimacy that a patient with CFS *I* ME feels.

He explained that CFS is not just a state of chronic fatigue (such as many people experience), but a truly debilitating state, associated with impaired memory / concentration, sore throat, adenopathy, myalgias, arthalgias, new headache, unrefreshing sleep, postexertional malaise, anorexia, nausea, drenching night sweats, intolerance of alcohol and pharmaceuticals that affect the central nervous system, and dizziness.

He reminded those present that objective, biological abnormalities can be found in patients with CFS, and that the medical literature of the past decade indicates that there are indeed such abnormalities.

Komaroff made the point that it is now evident that this illness is not simply an imaginary one, nor the result of anxiously amplifying normal bodily sensations. Komaroff dealt with the evidence of central nervous system (CNS) involvement in CFS: in his experience,
a majority of CFS patients have symptoms which could reflect an underlying CNS process, for example, difficulty with memory, concentration and balance; photophobia and paraesthesias; in addition, substantial objective evidence of abnormalities in the CNS is now available: MRI scans have revealed areas which may represent inflammation and *I* or demyelination.

Komaroff told the Conference that the signal abnormalities in CFS patients "most closely resemble those seen in AIDS encephalopathy".

Autonomic nervous system testing "frequently reveals abnormalities of the sympathetic and parasympathetic systems".

He then dealt with the evidence of chronic immune activation in CFS: Komaroff discussed this evidence, and concluded that a state of chronic immune activation could lead to the production of cytokines that disrupt neurotransmitter function, resulting in the symptoms of CFS.

He made the point that the state of chronic immune activation in CFS suggests the possibility of a chronic infectious process, saying that some physicians (including himself) believe that infectious agents may trigger and even perpetuate the symptoms of CFS; he referred to the evidence for a chronic viral infection as demonstrated by Suhadolnick, which showed an abnormality in an antiviral lymphocyte enzyme system (2-5A pathway), which is found to be chronically activated in patients with CFS.

Komaroff referred to the findings that many CFS patients have experienced atopic symptoms from childhood, and that the atopic symptoms often flare up in
CFS.

Komaroff stated that perhaps the most important nonpharmacologic intervention was to encourage patients to avoid physical or emotional stress, and to pace themselves.

He stated that it is antitherapeutic for the clinician to dismiss any patient's symptoms out of hand, especially in CFS, which is a "de-legitimating illness", as "patients often experience rejection by family, friends and physicians.. ..The illness is hardly 'imaginary'".

Chronic Faticiue Syndrome: A Challencie to the Clinical Professions Derek Pheby (Director, Unit of Applied Epidemiology, University of the West of England, Bristol, UK) *Physiotherapy: 1997:83:2:53-56*

"No-one who has experienced this illness, or who has had the responsibility of caring for a family member who has had the misfortune to suffer from it, can have any doubt not only about the extent of the real pain, suffering and distress that it can cause, but also as to the disastrous effect it can have on social relationships and life in the community".

"The most seriously affected individuals may be bed-ridden..., most or all of the time and can do little or nothing for themselves".

"In this illness, 'recovery' is very much a relative term: in follow-up studies.... after 48 years, eight out of ten patients continued to have some form of disability (Hyde &

Bergman 1991). This is in line with Ramsay (1986) who wrote that complete recovery is confined to one third of cases".

"Recent research has made it clear that the view that there were no specific changes demonstrable in patients with CFS has become untenable".

"The disturbances to the HPA axis in CFS differ markedly from those found in depression, as do brain vascular perfusion patterns".

"The overall costs associated with the syndrome are likely to be around £90 million per year (National Task Force Report, 1994, page 21). Given the tendency to chronicity. . .much of this cost is due to the need for long - term supportive care of patients".

"CFS/ME is a major challenge to all health care professionals".

Chronic Fatigue Syndrome —aetiological aspects Dickinson CJ. *Eur J Clin Invest: 1997:27:4:257-267*

"There is some evidence both for active viral infection and for an immunological disorder in the CFS. Many observations suggest that the syndrome could derive from residual damage to the reticular activating system (RAS) of the upper brain stem and *I* or to its cortical projections"

"Regional blood flow studies by SPECT have been more consistent (and) have revealed blood flow reductions in many regions, especially in the hind brain. Similar lesions have been reported after poliomyelitis and in multiple sclerosis —in both of which conditions fatigue is characteristically present".

Cardiac Involvement in Patients with Chronic Fatigue Syndrome as Documented with Holter and Biopsy Data in Birmingham, Michigan, 1991 - 1993 A.Martin Lerner et al. *Infectious Diseases in Clinical Practice 1997:6:327-333*

This study reports the prevalence of abnormal oscillating T-waves on Holter 24 hour monitoring in a consecutive case series of 67 CFS patients.

Resting 12 lead ECGs were normal, with the presence of labile T-wave abnormalities coming to light only with 24 hour Holter monitoring.

Repetitive T-wave flattening was a sensitive indicator of the presence of CFS, as every CFS patient (but only 22.4% of the controls) showed abnormal flattening or inversion on Holter monitoring.
Abnormal cardiac wall motion (at rest and on stress), dilatation of the left ventricle and segmental wall motion abnormalities were present. (Normal left ventricular resting

ejection fraction is 50%, but in CFS , the left ventricular ejection fraction — at rest and with exercise — of as low as 30% was seen).

Abnormal T-wave oscillations (T-wave flattening or inversion) of at least 25 normally conducted beats were necessary to be considered abnormal; they frequently appeared only with the advent of sinus tachycardia.

Two cardiologists unaware of the position of the patients reviewed the Holter tracings.

"This study confirms our earlier report (see *following item)* that CFS patients uniformly have abnormal oscillating T-wave flattenings and T-wave inversions by Holter monitoring.. ..as described here, abnormal Holter monitoring is important to the explicit diagnosis of patients with CFS (and) are a characteristic of CFS (and) appear to be an essential element to the pathologic physiology of the cardiomyopathy of the CFS".

New Cardiomyopathv: pilot study of intravenous gangiclovir in a subset of the chronic fatigue syndrome. Lerner AM et al *Infectious Diseases in Clinical Practice 1997:6:2:110-117*

This study involved a subset of CFS patients with oscillating repetitively abnormal aberrant T waves on Holter 24-hour electrocardiogram (ECG) recording. None of these patients could work or manage a household.

The type of abnormalities documented in the cardiac study "are not seen in normal persons leading a sedentary life".

Does the chronic fatigue syndrome involve the autonomic nervous system?
Freeman R and Komaroff AL *American Journal of Medicine 1997:102:4:357-364*

The aim of this study was to investigate the role of the ANS in the symptoms of CFS patients (selected if they had one of three criteria indicating ANS dysfunction).

The CFS subjects had significant increase in baseline and maximum heart-rate on standing and tilting.

Tests of the parasympathetic nervous system function were significantly less in the CFS group, as were measures of sympathetic nervous system function.

Deconditioning alone did not fully explain the documented ANA abnormalities.
89% of patients reported that an infectious illness had preceded the onset of CFS, and in 46%, the ANS symptoms occurred within four weeks of the infection: "a temporal pattern that is consistent with a postviral, idiopathic autonomic neuropathy".

Symptoms of ANA dysfunction are not related to psychiatric disorder.

A population-based incidence study of chronic fatigue
Lawrie SM, Pelosi AJ et al *Psychological Medicine 1997:27:343-353*

Longitudinal studies using appropriate measures have shown that physical attributions do not affect outcome.

Exercise limits in chronic fatigue syndrome
Lapp C. *American Journal of Medicine 1997:103:83-84*

This reports a trial involving 31 consecutive new CFS patients, which allowed them to reach their maximum oxygen consumption within 8 - 10 minutes of exercise.

The results showed that 74% of patients experienced worsening fatigue. None improved.

The average relapse lasted 8.82 days, although 22% were still in relapse at 12 days (when the study ended).

These findings suggest that, pushed to maximal exertion, patients with CFS may relapse.

Lapp advises his CFS patients to limit exercise to less than 5 minutes, followed by rest. This work-rest cycle may be repeated several times daily in order to maintain strength, flexibility and conditioning.

1998

Cardiovascular responses during a cognitive stressor before and after exercise in chronic fatigue syndrome versus sedentary healthy subiects SA Sisto, B Natelson et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS. Mass. USA 1998: Abstract:page 48

Patients with CFS complain of cognitive difficulties that worsen after exercise.

The purpose of this study was to determine if patients with CFS have similar cardiovascular responses (compared with sedentary controls) during a cognitive test battery, both before and after exercise.

The CFS group demonstrated a significantly lower change in systolic blood pressure compared with the sedentary controls.

Exercise produces the expected attenuation of the cardiovascular responses in the healthy group, but not so for the CFS patients.

This hyporesponsiveness may, in part, be responsible for CFS patients reporting detrimental effects of periods of psychological stressors or excess physical exertion.

CFS severity is related to reduced stroke volume and diminished blood pressure responses to mental stress Arnold Peckerman, Bejamin Natelson et al *Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS, Mass. USA 1998: Abstract page 47*

One plausible hypothesis of the pathophysiology of CFS is a disorder of circulation.

The present study examined whether cardiovascular homeostasis at rest and centrally-mediated haemodynamic responses to behavioural challenges are altered in CFS.

The results showed that in CFS patients, a lower stroke volume was highly predictive of illness severity: across three different postures, the most severely affected CFS patients were found to have a lower stroke volume and cardiac output compared with those with more moderate illness.

These findings suggest a low flow circulatory rate in the most severe cases of CFS; this may indicate a defect in the higher cortical modulation of cardiovascular autonomic control.

In the most severely affected, situations may arise where a demand for blood flow to the brain may exceed the supply, with a possibility of ischaemia and a decrement of function.

Respiratory symptoms and lung function testing in CFS patients P de Becker, K de Meirleir et al *Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS. Mass. USA 1998: Abstract page 104*

The purpose of this study was to report the prevalence of respiratory symptoms in a cohort of CFS patients.

The following respiratory symptoms were observed: cough, chest tightness, medical history of allergy, new onset of allergy; the major respiratory complaint was found to be a pronounced exercise-induced dyspnea.

In 60% of CFS patients, a marked bronchial hyper-responsiveness was present. (Bronchial hyper-responsiveness was defined as PD 20 *his* < 2 mg histamine).

CFS patients show a significant decrease in vital capacity (VC), possibly due to a significant increase of residual volume (RV).

The incidence of bronchial hyper-responsiveness in this group is remarkably high.

These observations can, at least partially, explain the respiratory symptoms in these patients.

Chronic Fatigue Syndrome: An Update A.L.Komaroff D.S.Buchwald *Annu Rev Med 1998:49:1-13*

Studies indicate that the illness is not simply a manifestation of an underlying psychiatric disorder, but rather is an illness characterised by activation of the immune system, various abnormalities of several hypothalamic pituitary axes and reactivation of certain infectious agents.

The most robust findings are increased numbers of CD8+ cytotoxic T cells that bear antigenic markers of immune activation on their cell surface, and depressed function of natural killer lymphocytes.

Other reported findings of immune activation are elevated levels of circulating immune complexes and immunoglobulin G, and higher frequencies of various autoantibodies.

More circumstantial evidence of a chronic viral infection in many CFS patients comes from reports of an abnormality in an antiviral lymphocyte enzyme system (the 2-5A pathway) which appears to be chronically activated in patients with CFS.

These reports provide strong evidence that CFS can be triggered by an acute infection that has the capacity to produce a chronic infection.

This paper concludes by affirming that “there is growing evidence that abnormal, objective biologic processes are present in many patients with CFS -- in particular, subtle abnormalities of the CNS, chronic activation of the immune system, and reactivation of several latent viruses”.

Muscle fibre characteristics and lactate responses to exercise in chronic fatigue syndrome Russell JM Lane, Leonard C Archard et al *JNNP 1998:64:362-367*

The object of this study was to examine the proportions of types I and II muscle fibres and the degree of muscle fibre atrophy and hypertrophy in patients with CFS in relation to lactate responses to exercise, and to determine to what extent any abnormalities found might be due to inactivity.

Muscle fibre histometry in patients with CFS did not show changes expected as a result of inactivity

The authors note that one of these patients had an inflammatory infiltrate, and it would seem that inflammation and class I MHC expression may occur in biopsies from patients with CFS.

The authors note that this is of some interest, as they have argued previously that some forms of CFS may follow a previous virally-mediated inflammatory myopathy.

On symptoms and life events surrounding the onset of chronic fatigue syndrome
Evengard B et al *Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS, Mass. USA: 1998: Abstract page 32*

This study was aimed at describing the sequence of psychosocial events and infections preceding the onset of CFS (related to the temporal development of crucial symptoms).

Sixty seven percent of the CFS patients had a clearly negative life event preceding infection, which preceded CFS onset.

Gastrointestinal Manifestations of Chronic Fatigue Syndrome: Symptom: Perceptions and Quality of Life Herbert Hyman Thomas E Wasser *JCFS 1998:4(1):43-52*

The authors conclude that the classification of irritable bowel syndrome (IBS) should be modified to include a subset of patients who have a combination of CFS and lBS.

They enumerate not only functional gastrointestinal (GI) complaints, but also other abdominal complaints, particularly neurologic.

They point out that in CFS, immunologic abnormalities are regularly found, and that there are more lymphocytes associated with the Gl tract than any other site in the human body.

Since the gut mucosa contains immunologically active lymphoid tissue, the authors believe that a pattern of immune dysfunction exists in CFS in which immune products are transmitted to the gut via the lymphatic system, reacting on both the lumenal contents and intestinal motor system, and that the GI lymphatic system not only has an effector function, but also transmits characteristic CFS immune dysfunction to other organs.

The authors also suggest that oral antigens could be similarly effective in CFS patients by way of the immunological activity of the gut mucosa.
Some CFS patients had abdominal wall pain due to unilateral segmental neuropathy.

In summary, this study demonstrated three primary findings: (I) CFS patients showed significantly more symptom dysfunction than those in the functional bowel disease (FBD) group; (ii) CFS patients had significantly lower Quality of Life scores than the FBD group and (iii) since differences occur between CFS and FBD patients, the classification of lBS should be modified to include a subset of patients who have a combination of CFS and lBS.

Chronic Fatigue Syndrome in Children and Adolescents: A Review. Karen M Jordan, Leonard A Jason et al *Journal of Adolescent Health 1998:22:4-18*

The majority of studies concerning CFS have concentrated on adults, but the illness does strike younger individuals, and the case definitions do not address the appropriateness for the paediatric population. The lack of specificity to the unique characteristics of children and adolescents is pervasive in much of the research literature.

Several authors reported a preponderance of acute onset with viral-type illness in children and adolescents.

Many previous epidemiological studies (one of Wessely's studies is cited) have relied on physician referral, when (those) physicians are sceptical of the validity of CFS as a true illness.

Repetitive treatment-seeking is often necessary before a diagnosis of CFS is made: children may be less able to seek care persistently, so the prevalence rate in those under 18 years has undoubtedly been minimised.

The authors describe the Cheney proposition *(Cheney PR. Proposed pathophysiological mechanism of CFIDS. CFIDS Chronicle: 1994:7: 1-3)* that the common symptoms of CFS (eg. hyperreflexia, abnormalities of vestibular function, palpable and slightly enlarged discoid shaped lymph nodes, predominantly left-sided tender posterior and cervical lymph nodes) suggest a connection between immune activation and central nervous system injury: as alpha-interferon can be neurotoxic, particularly to the limbic structure and the serotonergic pathways (via opioid receptors), this may account for the abnormalities in corticotrophin-releasing hormone (CRH), and these deficiencies then contribute to a positive feed-back loop which maintains immune activation.

In addition, the decrease in TRH production could lead to reduced cellular metabolism, including impaired oxygen consumption during exercise, which is consistent with mitochondrial dysfunction.

The authors note that there has been minimal controlled study of psychiatric status for children and adolescents with CFS. However in one study, adolescents with CFS received higher scores of psychiatric comorbidity, but on further examination of the somatic complaint items, it was found that this scale was confounded by the presence of many items related to CFS symptoms (eg. headaches, pain and feeling sick).

The authors state that the overlap of CFS symptoms with those of psychiatric disorders has been found to lead to an overdiagnosis of psychiatric disorder in adult CFS populations.

The authors note that a list first supplied by Komaroff provides four discriminating characteristics of fatigue and symptoms which should assist the clinician in distinguishing between CFS and malingering or somatoform disorders, and these include symptoms which are rarely found in paediatric general practice.

The authors note that the perceived causal role of depression in CFS may have been inflated in some studies owing to frequent errors.

They note that the DSM IV criteria for depression do not include any of the primary complaints of patients who present with CFS.

Further, the DSM IV criteria for somatisation do not mention fatigue symptoms.

The DSM IV states that individuals with somatisation disorder describe their complaints in a colourful, sensational and emotional manner, with specific factual information missing.

On the contrary, people with CFS describe their symptoms clearly and concisely.

Minimal work has been done in the formal assessment of coping with illness, level of disability or quality of life issues in children and adolescents with CFS.

Paediatric patients may require assistance obtaining special services or accomodations from their school.

The authors note that several authors (Sharpe and Wessely are named) have proposed the use of cognitive behavioural therapy (CBT), and note that while the Sharpe study may be criticised for its poor subject selection methods, no other studies have reported the effectiveness of CBT with child or adolescent populations.

Several authors have conducted follow-up studies with paediatric CFS patients; most reported improvement or recovery in over 50% of the patients studied, but the present authors note that some children continued to experience significant disability, and that it is possible these children who do not improve represent a unique subset of paediatric CFS, perhaps having a more severe form of the illness, including more severe neurologic symptoms such as myoclonus, paraesthsia and seizure-Iike episodes.

Much of the current literature is confused by the lack of paediatric case definition.
CFS in children and adolescents remains dramatically understudied.

It is imperative that criteria specific to children and adolescents be adopted and used as a standard in future research.

Brain SPET in Chronic Fatigue Syndrome D.di Giuda, D.Racciatti et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS, Mass. USA: 1998: Abstract page 112

CFS is a severely disabling illness; this study was designed to investigate possible changes in the brain perfusion of patients with CFS.

Regional brain perfusion impairment (mainly hypoperfusion) was found in 83.9% of CFS patients.

In 30.8%, a concurrent fibromyalgia syndrome was present. A total of 147 brain regions showed abnormal 99mTc-HMPAO uptake.

This study confirmed previous reports of brain perfusion impairment in CFS, providing objective evidence of central nervous system dysfunction.

Impaired associative learning in chronic fatigue syndrome Servatius RJ, Natelson BH et al *Neuroreport: 1998:9:1153-1157*

The researchers tested patients with CFS in protocols designed to measure memory reactivity and acquisition of the classically conditioned eyeblink response.

The authors conclude that their data suggest organic brain dysfunction within a defined neural substrate in CFS patients.

Relationship between SPECT scans and buspirone tests in patients with ME *I*CFS
Richardson J and Costa DC *JCFS 1998:4:3:23-38*

The SPECT scans revealed that all CFS patients studied had hypoperfusion in the brain: 62% in the brain stem and 51% in the caudate nuclei.

According to the researchers, these findings provide “actual evidence of neurological dysfunction” in ME *I* CFS.

Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data
Tirelli U. et al *American Journal of Medicine 1998:105:3A: 54s-58s*

The PET images examined 22 cortical and subcortical areas. PET is better than SPECT at detecting small structures such as the brain stem.

The scans revealed significantly reduced glucose metabolism in the brainstem of patients with CFS compared with depressed patients and healthy controls. The area particularly affected in the brainstem was the pons. There was also significant hypometabolism in the right mediofrontal cortex in the CFS patients.

Hypometabolism of the brainstem has not been documented in any psychiatric disorder assessed to date.

Neurally Mediated Hypotension and Chronic Fatigue Syndrome
Peter C Rowe & Hugh Calkins *Am J Med 1998:105: (3A):15S-21S*

This article discusses selected issues in the clinical overlap of CFS and autonomic dysfunction.

The authors note that frequently in CFS, patients have symptoms of lightheadedness (88%); cognitive difficulties *I* problems thinking and concentrating (47%); blurred vision (47%); tremulousness (38%); pallor (31%) and anxiety (29%), and that these neurocognitive symptoms have been attributed to cerebral hypoperfusion.

That fatigue can be associated with neurally mediated hypotension has been appreciated since 1932, when Sir Thomas Lewis demonstrated that a long period of fatigue could follow a single episode of vasovagal (or neurally mediated) hypotension.

One of the patients who prompted the authors' investigation was a 16 year old girl who described becoming tired, shaky, lightheaded and pale after walking more than 10 minutes: one notable physical finding was that her legs and arms developed a purple discolouration after a short period of quiet standing, which is indicative of abnormal venous pooling.

In this study, all the CFS patients but none of the controls developed orthostatic symptoms during the first stage of the testing, suggesting that orthostatic intolerance may be a defining feature of CFS.

Three factors which predispose to the development of NMH are a low resting blood volume, excessive pooling of blood in the dependent vessels, and excessive loss of plasma volume during upright posture, all of which can decrease venous return to the heart.

In those with abnormal responses to upright tilt, when cardiac output is consequently decreased, there seems to be a failure to mobilize blood effectively from the dependent splanchnic and limb vasculature: several groups have identified impaired vasoconstrictor responses in the forearm and splanchnic bed, and in microvascular flow to the skin.

Among the neuroendocrine changes that accompany the orthostatic intolerance are an increase in epinephrine, vasopressin, ß-endorphin and vasoactive intestinal polypeptide.

Factors that can contribute to early activation of the vasovagal reflex include stress and sodium depletion.

Conditions with an increased histamine release can also cause a decreased return of blood to the heart.

Such an inappropriate venous return could provoke worse orthostatic tolerance in response to common everyday cognitive stress, which could provide an explanation for why some patients describe worse fatigue after reading or concentrating.

Virtually *all* CFS patients (regardless of their haemodynamic response) have their symptoms provoked by standing upright.

The authors note that there is a high prevalence of allergic disease in those with CFS, and suggest that with an association between CFS and NMH, one would expect to find a mechanism by which allergic disease increases the activation of this reflex pathway: other workers have shown that both viral infection and allergic reactions to food antigens increase the excitability of mechanically sensitive vagal afferents in the airway.

The ability of allergen exposure to enhance the discharge of mechanically sensitive fibres, including C-fibres, provides a potential link between these clinical situations and the development of NMH in CFS patients with allergy, suggesting that efforts to prevent activation of NMH would need to prevent exacerbation of food and inhalant allergies in those with CFS.

Low levels of serum acylcarntine in chronic fatigue syndrome and chronic hepatitis type C. but not seen in other diseases. Kuratsune H et al *International Journal of Molecular Medicine 1998:2:1:51-56*

This study found significantly lower serum acylcarnitine (ACR) in CFS patients but not in controls.

It was not present in other medically ill populations such as patients with haematological malignancies, chronic pancreatitis, hypertension or diabetes.

ACR may have an effect as an antioxidant and may be linked to the production of cytokines.

These findings indicate that serum ACR deficiency may be a characteristic of CFS.

Secretion of growth hormone in patients with chronic fatigue syndrome Berwaerts J et al *Growth Hormone and IGF Research 1998:8:127-129*

Serum IGF-l was significantly lower in patients with CFS than in controls.

Adrenal size in chronic fatigue syndrome Teh J, Scott L, Dinan E et al
Radiology 1998:209P (Suppl):411-412

A CT scan revealed that the right and left adrenal glands of CFS patients were reduced by 50% when compared with healthy people.

Increased resting energy expenditure in the chronic fatigue syndrome
Watson WS, Chaudhuri A, Behan P0 et aI *JCFS 1998:4:4:3-14*

When individual resting energy expenditure (REE) was predicted on the basis of total body potassium values, 45.5% of the CFS patients tested had resting energy expenditure above the upper limit of normal, suggesting that there is upregulation of the sodium-potassium pump in CFS.

There was no evidence that the results were due to lack of activity (which would have affected total body water estimates).

Parallels between post-polio fatigue and chronic fatigue syndrome: a common pathophysiology? Bruno RL et al *Am J Med 1998: 105 (3A) 66S-73S*

Post-polio fatigue is characterised by subjective reports of difficulty with attention, cognition, and maintaining wakefulness. These symptoms resemble those reported in nearly two dozen outbreaks of post-viral fatigue syndrome (PVFS) that have recurred this century and which are related clinically, historically, anatomically or physiologically to polio virus.

This article reviews studies which relate the symptoms of post-polio fatigue and chronic fatigue syndrome to clinically significant deficits on neuropsychologic tests of attention, histopathologic and neuroradiologic evidence of brain lesions, impaired activation of the HPA axis, increased prolactin secretion, and EEG slow-wave activity.

A common pathophysiology for post-polio fatigue and CFS is described.

Alteration of spatial-temporal parameters of gait in Chronic Fatigue Syndrome
Saggini R et al *J Neurol Sci 1998:154:1:18-25*

CFS has been widely studied and a lot of information is available in the literature regarding immunological, virological, neuroendocrinal and psychiatric aspects of this disease, and great attention has been paid to the alteration of muscular function in CFS.

The aim of this work was to study the gait of CFS patients to see if there are objective measures which can better characterise the pathology.

Comparison with reference data from healthy controls revealed significant abnormalities.

The abnormalities were present as from the beginning of the gait, which indicates that they are unlikely to be caused by rapidly increasing fatigue.

These findings strengthen the notion of direct involvement of the central nervous system in CFS.

A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome Peterson PK et al *Arch Intern Med 1998:158: (8):908-914*

At baseline, study participants reported symptom severity greater than 5 for most symptoms and all had evidence of marked functional impairment.

Five patients withdrew from the trial.

The incidence of adverse experience was similar in patients and controls.

The authors conclude that low dose fludrocortisone (0.1 - 0.2mg for six weeks) does not provide sufficient benefit to be evident in a blinded trial of unseIected patients with CFS.

Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomised controlled trial Mckenzie R, Dale J, Demitrack M et al *JAMA 1998:280: (12): 1061-6*

The object of this study was to evaluate the efficacy and safety of low-dose oral hydrocortisone as a treatment for CFS (oral hydrocortisone, 13 mg /m2 of body surface area every morning and 3 mg /m2 every afternoon for approximately 12 weeks).

The authors conclude that the degree of adrenal suppression precludes the practical use of hydrocortisone in CFS.

Immunological Status Correlates with Severity of Physical Symptoms in Chronic

Fatigue Syndrome Patients S.Wagner, N.Klimas et al *Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS 1998: Mass. USA. Abstract page 28*

The purpose of this study was to investigate the relationship between immunologic status and physical symptoms in CFS patients.

The findings suggest that the degree of cellular immune activation is associated with the severity of CFS physical symptoms.

Specifically, elevations in the T-helper / inducer cells, activated T-cells, activated cytotoxic / suppressor T-cells, and CD4 *I* CD8 ratio are associated with greater disease severity.

Furthermore, reductions in T-suppressor *I* cytotoxic cells also appear related to greater severity of CFS physical symptoms and illness burden, suggesting that greater symptoms are associated with lower availability of regulatory T-ceIIs.

A study of the Immunology of the Chronic Fatigue Syndrome: Correlation of Immunologic Parameters to Health Dysfunction l.S.Hassan, W.Weir et al. *Clin Immunol lmmunopathol 1998:87:60-67*

Surface and intracellular immunologic and apoptotic markers and functional lymphocyte assays after stimulation with anti-CD3 *I* anti-CD28 antibodies or phytohaemagglutinin (PHA) were studied.

Patients with increased HLA-DR expression had worse pain and poorer physical functioning scores.

The increased expression of Class II antigens and the reduced expression of the co-stimulatory receptor CD28 (which is a marker for terminally differentiated cells) lend further support to the concept of immunoactivation of T-lymphocytes in CFS and may be consistent with a viral aetiopathogenesis in CFS.

The authors demonstrated changes in different immunological parameters, each of which correlated with particular aspects of disease symptomatology and measures of disease severity.

Co-incidental splenectomy in chronic fatigue syndrome Brian J Miller et al
JCFS 1998:4(1): 37-42

The authors describe the removal of a ruptured spleen in a female with CFS following a road traffic accident.
At operation, the splenic parenchyma was unusually spongy and friable.

There was a generalised infiltration of the splenic sinuses by atypical lymphoid cells. These cells appeared blastic and had large, vesicular nuclei, multiple large nucleoli and a moderate amount of dense, eosinophilic cytoplasm.

In immunohistochemical studies, they were strongly reactive for the T-lymphocyte markers CD45RO and CD43.

In addition to this cellular infiltrate, there was a reduction in the volume of the white pulp.

Histological examination of the spleen revealed chronic inflammatory changes of uncertain aetiology.

These histopathological changes in the spleen of a patient with CFS have not been described before.

The reduction in white pulp and infiltration of the splenic sinuses by atypical lymphoid cells are not features of traumatic rupture, and suggest a chronic inflammatory process likely to be associated with CFS.

(At the Second World Congress on Chronic Fatigue Syndrome and Related Disorders, Brussels, 9-12th September 1999, Dr L Lambrecht from Belgium spoke on "Chronic Fatigue Syndrome: Clinical, Immunological and Neuroimaging Correlations in 500 Patients', noting that splenomegaly was reported in 29% of CFS patients, saying that this finding has not previously been reported).

T-Lymphocytes in CFS -- in vitro reaction to mutagens I Hauspie, K de Meirleir et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS 1998: Mass. USA. Abstract page 70

Many studies in CFS patients suggest a virally-triggered onset, associated with an abnormal immune function.

The results from this study add information to the existing knowledge of intracellular abnormalities in CFS, and point towards abnormalities in intracellular protein metabolism, with increased sensitivity to alcohol.

The authors believe that lymphocytic cell membrane permeability is altered in CFS.

Lvmph node morphology and phenotype in chronic fatigue syndrome Nancy Klimas et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS 1998: Mass, USA. Abstract page 73

CFS is an illness which is associated with immune dysfunction, including abnormalities in the function and activation status of peripheral blood lymphocytes. There has been no study of the lymph node compartment in this illness.

The authors conclude that the distribution of lymphocyte subsets in the lymph nodes in CFS patients offers confirmation regarding the immunopathogenesis of CFS.

The data here presented indicate a preponderance of activated T-cells that is even higher than that reported in peripheral blood.

The findings are compatible with a chronically activated immune status in this patient group.

CD4 T Lymphocytes from Patients with Chronic Fatigue Syndrome have Decreased Interferon - γ Production and Increased Sensitivity to Dexamethasone Jeroen Visser et al *The Journal of Infectious Diseases 1998:177:451-4*

To the authors' knowledge, this study was the first to compare properties of purified CD4 T cells from CFS patients with those of cells from healthy controls.

The CD4 cells were studied to determine whether they have an altered sensitivity to dexamethasone (DEX).

CD4 T cells from CFS patients produced less interferon -ÿ than did the cells from controls, indicating an increased sensitivity to DEX.

The authors suggest that their observation of low interferon - ÿ production in CFS might be due to an increased sensitivity of the CD4 T cells for glucocorticoids, which are known to modulate T cell responses.

Decreased immunoreactive beta-endorphin in mononuclear leucocytes from patients with chronic fatigue syndrome Conti F et aI *Clinical & Experimental Rheumatology 1998:16:6:729-732*

Beta-endorphin concentrations were measured in peripheral blood mononuclear cells (PBMC) by radioimmunoassay performed with antibodies specific for the C-terminal portion of human beta-endorphin.

Beta-endorphin concentrations in the PBMC of CFS patients were significantly lower than in the healthy subjects.

Beta-endorphin concentrations in PBMC seem to mirror the central nervous system homeostasis of the opioid, thus the fatigue and weakness typical of CFS could be related to low beta-endorphin concentrations at the CNS level.

The in vitro immunomodulatory effects of glyconutrients on peripheral blood mononuclear cells of patients with chronic fatigue syndrome See,DM et al *Integrative Physiological and Behavioural Science 1998:33:3:280-287*

A glyconutrient compound was added to PBMC isolated from 90 normal controls and 91 patients with CFS.

Cell surface expression of the glycoproteins CD5, CD8 and CD11a were significantly lower in patients with CFS compared with normal controls.

Furthermore, natural killer (NK) cell function was reduced in CFS patients.

Importantly, apoptosis was significantly higher in patients with CFS, but the percentage of apoptotic cells was significantly decreased in PBMC of CFS patients which had been incubated for 48 hours with glyconutrients.

Thus glyconutrients improved immune parameters in vitro in patients with CFS.

Chronic fatigue in overlap syndromes Abhijit Chaudhuri Peter Behan
Neurology 1998:1:2:16-20

The authors state that CFS is a disabling neurological illness which may be precipitated by infections, toxins, and physical and mental stress.

They point out that only when a poliomyelitis epidemic swept California in the summer of 1934 was CFS distinguished as a separate epidemic illness, when it was called ‘atypical poliomyelitis’.

Most CFS cases now occur sporadically; clinical symptoms include generalised muscular aches and pains (fibromyalgia), weakness, sleep disorder, impaired memory and mental concentration, paroxysmal (usually nocturnal) sweating, intermittent dysequilibrium, mild myoclonus, cervical adenopathy (early in the illness),vertigo, palpitations and angina-like chest pain.

The authors state that the organic nature of CFS soon became apparent from detailed study of symptoms and from neuroendocrine tests.

The authors state that in a number of diseases, fatigue similar to that in CFS may be the only symptom before other signs become apparent: multiple sclerosis (MS), chronic inflammatory demyelinating polyneuropathies (CIDP), sarcoidosis and haemachromatosis are common examples where fatigue can antedate other symptoms; such CFS-associated or CFS-overlap syndromes can be grouped into four divisions:

syndromes commonly associated with postviral or idiopathic CFS (eg. dysequilibrium syndrome, Gilbert's disease, atopic disorders, including gluten sensitivity, syndrome X and irritable bowel syndrome)

CFS-like syndromes following exposure to chemicals (eg. after ciguatera fish poisoning, or following exposure to low dose organophosphate compounds, organochlorine exposure, multiple chemical sensitivities, fatigue induced by medication, including anaesthetics)

medical or neuropsychiatric diseases where the severity of the fatigue is independent of the underling illness (eg.sarcoidosis, Sjogren's syndrome, SLE and other vasculitides, demyelinating neuropathies, Parkinson's disease, metabolic myopathies, HIV infection, post-head injury)

other CFS-like syndromes, where the precipitating factor is uncertain (eg.Gulf War syndrome, sick building syndrome, a CFS-like syndrome following silicone breast implants).

The authors state that Syndrome X is characterised by typical anginal chest pain but with a normal coronary angiogram. Angina-like chest pain, similar to Syndrome X, is a common symptom in CFS patients: the two syndromes share many similarities, including an identical clinical course.

A similar exaggerated GH-release response is seen in patients with chronic low-dose exposure to OPs, who develop a neurobehavioural syndrome identical to CFS.

The irritable bowel syndrome which occurs in CFS is identical to 'idiopathic' lBS.

Cases of CFS may develop after physical trauma.

CFS has bee reported in multiple chemical sensitivity, and over-trained athletes may develop a syndrome indistinguishable from CFS.

In summary, CFS should be considered multifactorial in origin, with infection and stress being the two most common triggers.

The mechanism of fatigue in various neurological disorders, including CFS, may be related to an abnormal cell membrane ion channel and / or membrane-associated ATPase function.

1999

Demonstration of delayed recovery from fatiguing exercise in chronic fatigue syndrome
Lorna Paul,Leslie Wood,Wilhemina M.H.Behan & William M.Maclaren
European Journal of Neurology 1999:6:63-69

The purpose of this study was to try to confirm the observations that patients with CFS complain consistently of delay in recovery of peripheral muscle function after exercise.

The use of 31 P-nuclear magnetic resonance (31 P-NMR) has now provided positive evidence of defective oxidative capacity in CFS.

Patients with CFS reach exhaustion more rapidly than normal subjects, in keeping with an abnormality in oxidative metabolism and a resultant acceleration of glyolysis in the working skeletal muscles.

When the rate of resynthesis of phosphocreatinine (PCr) following exercise is measured, this abnormality is confirmed

The authors' study provides a conclusive demonstration that recovery is significantly delayed in patients with CFS.

It also supports the fact that patients with CFS produce maximum voluntary contractions during exercise. The authors are confident that the differences observed in recovery in this study represent true effects.

The results demonstrate that patients with CFS fail to recover properly from fatiguing exercise and that this failure is more pronounced 24 hours after exercise.

Some of the patients demonstrated more severe effects than others.

Indeed, while the recovery of force in the controls was complete by 200 minutes post-exercise, "an even further decline in force" was observed among the CFS group at 24 hours post-exercise.

This delayed recovery is unlikely to be the result of de-conditioning.

The findings support the clinical complaint of delayed recovery after exercise in patients with CFS.

The authors note that recent experiments by others *(Bouwer & Packer: Corticospinal excitability in patients in patients diagnosed with CFS. Muscle Nerve 1994: 1210-1212; Samii et al: Decreased post-exercise facilitation of motor-evoked potentials in patients with CFS or depression. Neurology 1996:1410-1414)* have demonstrated a significant reduction in motor evoked potentials following exercise in CFS patients compared with controls. This is in keeping with a reduction in the

excitability of the motor cortex and could account for a reduction in voluntary motor output leading to the decline in muscle force observed in this study.

Chronic Fatigue Syndrome is a Acquired Neurological Channelopathy
Abhijit Chaudhuri & Peter Behan *Hum Psychopharmacol Clin Exp 1999:14:7-17*

Review article noting that the fatigue in CFS is distinct from the fatigue of neuromuscular disorders but similar to that found in disorders of the central nervous system such as multiple sclerosis, Parkinson's disease and multiple system atrophy.

The authors note that many symptoms of CFS, including severity of fatigue, may be induced by physical trauma and stress.

In this paper, the authors propose dysfunctional ion channels in the cell membrane as the key abnormality in CFS, which may also be responsible for the altered neuroendocrine function found in CFS.

A significant proportion of patients with CFS suffer from irritable bowel syndrome.

Autonomic dysfunction in CFS is also well recognised.

CFS patients have a supersensitivity of cortisol response to exogenous ACTH:
both physical trauma and emotional stress (such as bereavement) can precipitate CFS, directly activate the HPA axis and modify the immune system. Chronic activation of the HPA axis may cause a relative decrease by the adrenals of delta 3 - adrenal androgens. This process, in turn, may alter the helper Tcell phenotype in chronically affected patients.

Cytokine levels increase during stress: it has been shown clearly that breakdown of the blood-brain barrier (BBB) can occur during periods of stress.

At the cellular level neurochemicals use second messengers and ion channels for their desired actions.

It is therefore possible that neurochemical abnormalities can lead to alterations in the normal receptor and ligand-gated ion channel function.

Abnormal ion channel functions as the mechanism of neurological disorders now constitute a new group of diseases termed *channelopathies.*

Changes in the ion channel function from time to time offer a rational basis to explain the fluctuating fatigue and related symptoms in CFS. Known channelopathies provide excellent examples of neurological conditions where the symptoms are periodic, fluctuating, and are induced by physical activities, stress and fasting.

If the sodium channels are blocked in the open mode, this causes entry of sodium into neural tissues and muscles. This ingress of sodium is followed by water, which in turn leads to swelling of the neural tissues, a phenomenon observed both electron microscopically and by laser scanning microscopy.

Acquired ion channel abnormalities in myocardium could explain the pathogenesis of Syndrome X and may form the basis of cardiac dysfunction in both Syndrome X and in CFS — a highly significant proportion of CFS patients have cardiomyopathy, as shown in the epidemiological study by Lerner et al

Ion channel abnormality leading to selective neuronal instability may be the common disease mechanism in CFS and other disorders affecting brain function such as migraine and epilepsy.

The authors believe that CFS is *acquired* rather than inherited, making any therapeutic attempts to correct an ionophoric defect difficult.

Dehydoepiandrosterone (DHEA) response to i/v ACTH in patients with chronic fatigue syndrome De Becker P, de Meirleir K et al *Hormone and Metabolic Research 1999:31:1:18-21*

In order to investigate the dynamic response of the adrenal glands, the researchers measured serum levels of DHEA at intervals during 60 minutes after ACTH stimulation. Patients in the study were severely affected, with no psychiatric illness.

The patients had a blunted serum DHEA response curve to i/v ACTH injection.

This observation adds to the large amount of evidence of endocrinological abnormalities in CFS.

Relative glucocorticoid deficiency might contribute to the overall clinical picture in CFS and could explain some of the immunological disturbances observed in this syndrome.

Chronic fatigue syndrome. Pagani M and Lucini D. *Clinical Science 1999:1:117-125*

In CFS there are reported disturbances in autonomic activity and in other homeostatic mechanisms, such as hormonal and immune systems.

There are alterations in cardiovascular autonomic control, as can be assessed by spectral analysis of R-R interval and systolic arterial pressure variability.

Indices of sympathetic modulation could provide quantifiable signs of the interaction between the patients' efforts and their environmental demands, independently of self

description; this could provide convenient measurable outcomes, both for diagnosis and treatment titration.

Chronic fatigue syndrome: assessing symptoms and activity level. Jason LA et al
J Clin Psychol 1999:55:4:411-424

Current approaches to the diagnosis and assessment of CFS rely primarily on scales which measure the occurrence of various symptoms in CFS.

Such approaches do not provide information on either the severity of symptoms or on the fluctuations in symptom severity, or on activity level over time. As a result, these measures do not reflect the complexities and the inter-reactions among symptoms.

By obscuring the fluctuating nature of CFS and its high variability, commonly used assessment procedures may prevent health care professionals from understanding the complexities of this disease.

For illustrations of papers from 1999 to date (2001) which document significant biomarkers of organic pathology in CFS/ME, see the following sections on specific medical disciplines, eg. immunology, neuroendocrinology, virology, brain imaging, vascular medicine and the section on general papers on ME / ICD-CFS which document muscle abnormalities etc.

See also CFS Conference abstracts (eg. Brussels 1999; Seattle, January 2001) in the following sections.