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Chronic Fatigue Syndrome
An Update

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Contents

Abstract

The chronic fatigue syndrome is characterised by a fatigue that is disproportionate to the intensity of effort that is undertaken, has persisted for 6 months or longer, and has no obvious cause. Unless there has been a long period of patient– or physician– imposed inactivity, objective data may show little reduction in muscle strength or peak aerobic power, but the affected individual avoids heavy activity. The study of aetiology and treatment has been hampered by the low disease prevalence (probably <0.1% of the general population), and (until recently) by a lack of clear and standardised diagnostic criteria. It is unclear how far the aetiology is similar for athletes and nonathletes. It appears that in top competitors, overtraining and/or a negative energy balance can be precipitating factors. A wide variety of other possible causes and/or precipitating factors have been cited in the general population, including psychological stress, disorders of personality and affect, dysfunction of the hypothalamic-pituitary-adrenal axis, hormonal imbalance, nutritional deficits, immune suppression or activation and chronic infection. However, none of these factors have been observed consistently. The prognosis is poor; often disability and impairment of athletic performance are prolonged. Prevention of overtraining by careful monitoring seems the most effective approach in athletes. In those where the condition is established, treatment should aim at breaking the vicious cycle of effort avoidance, deterioration in physical condition and an increase in fatigue through a combination of encouragement and a progressive exercise programme.

The chronic fatigue syndrome (CFS)[1-5] is characterised by a fatigue that is excessive relative to the level of physical activity that is attempted, with no obvious cause. The condition shows some similarities to overtraining,[6-8] and is a well recognised problem among high performance athletes,[9-11] perhaps because extreme physical effort is demanded repeatedly of such individuals and their performance is closely monitored. Chronic fatigue can and does develop in nonathletic individuals, also, although there seem to be some points of difference from the syndrome as observed in top competitors. In addition to, and (in the athlete) interacting with excessive training, potential causes and/or precipitants include a primary or secondary disorder of affect and personality, severe emotional stress,[12] involvement in war with associated exposure to toxic vapours,[13] trauma, surgery, exhaustion of the hypothalamic-pituitary-adrenal (HPA) axis and hormonal dysfunction, a nutritional deficit, reactions to allergies and infections, with activation or suppression of immune function (table I). Sometimes, there has been no clear precipitant.[14]

Table I. Postulated causes and/or precipitants of chronic fatigue syndrome

Primary or secondary disorder of personality
Primary or secondary disorder of affect
anxiety
depression
Autonomic dysfunction
altered balance of sympathetic and parasympathetic tone
postural hypotension
Hormonal disturbances
Nutritional deficits
Immunosuppression
Infection
External factors
physical or emotional stress
overtraining
secondary deconditioning
trauma
injury
high-altitude training

Accompanying symptoms seem influenced in part by the specialisation of the physician consulted. Complaints may suggest involvement of the psyche, a primary or secondary disorder of affect, with associated cognitive deficits, confusion headaches and disturbed sleep. The muscles and joints often show post-exertional weakness, fatigue and arthralgia. Sometimes there is also a history of viral infection.[15,16] There may be complaints of sore throat, fever or flu-like symptoms,[17,18] and a painful lymphadenopathy suggests involvement of the immune system. Nevertheless, it remains unclear whether immune dysfunction or chronic disease is the primary problem in such cases.[19]

An attempt was made to distinguish athletic overtraining from CFS in 1991,[20] although a second review of overtraining by the same group of authors failed to examine its possible relationship to CFS. A more recent monograph on overtraining made no more than brief reference to CFS.[7] The topic of CFS has been examined from the perspective of exercise therapy,[4] but the issue of the competitive athlete was not discussed in this report. There have also been several detailed clinical reviews.[1,15,21-30] However, a 'review of reviews' concluded that the selection of topics and articles was unduly influenced by the specialty of their respective authors.[31] Moreover, it still remains unclear how far the condition is pathologically uniform,[25,28] and some authors still regard it as a 'nondisease',[32] created by the patient or the attending physician.[33]

The present review provides an update from the perspective of the sports physician. It focuses particularly upon material from the 595 entries for Chronic Fatigue Syndrome listed in Medline over the period 1996 to 2000, but it is supplemented by reports drawn from Sport Discus and the author's extensive personal files. In almost all instances, published reports are based on small case-control studies, controls generally being healthy individuals matched for age and gender, but not always for habitual physical activity.

1. Diagnosis and Prevalence of the Disorder

1.1 Diagnosis

The apparent prevalence of the disorder and indeed its characteristics depend largely on the criteria that are adopted for diagnosis and the specialisation of the examining physician. For example, if an athlete with CFS is examined by a sports physician, it seems likely that some evidence of overtraining will be reported.

In the general population, there is substantial overlap between CFS and unexplained chronic fatigue.[34] Other potentially overlapping conditions include fibromyalgia, Sjögren's disease (a human lymphocyte antigen-linked immunological disease) and depression. One survey from Ireland found only 58% of general practitioners accepting CFS as a distinct entity, with 34% undecided, and 8% rejecting such a concept.[34]

1.1.1 Distinction from Overtraining

Fatigue is to be anticipated in athletes who are undertaking a high volume of training, and CFS seems likely to cause one definition of overtraining (an inability to perform at a previously demonstrated optimum despite a continuation of intensive training).[35] Thus, in an athletic population it is often quite difficult to distinguish between a normal level of fatigue, overtraining, fatigue that indicates the onset of some specific medical problem and CFS.[20,36]

Nevertheless, there seem some points of distinction between chronic fatigue and overtraining, and indeed CFS can arise in relatively sedentary individuals. In nonathletes who are affected by CFS, evidence of muscle damage is usually slight or nonexistent.[4] In contrast, muscle tissue damage, disturbances of the HPA axis, hormonal and nutritional depletion, immunosuppression and infection can all result from overtraining in a top athlete, and these factors can all precipitate or contribute to manifestations of CFS in vulnerable individuals.

1.1.2 Distinction from Fibromyalgia

There is considerable overlap between CFS and the fibromyalgia syndrome (FMS).[37,38] An analysis of 74 FMS cases found that 58% of women and 80% of men met the full Centers for Disease Control (CDC) criteria for CFS.[39] Evengard and associates[40] suggested that one useful distinguishing criterion was an elevated level of substance P in the cerebrospinal fluid in FMS, but not in CFS.

1.1.3 Standardisation of Diagnostic Criteria

An attempt at standardisation of diagnostic criteria was made by the CDC in 1988.[2] In Britain, a consensus proposal for a revised set of criteria was developed at Oxford,[41] and a simplified definition was also proposed in the US in 1994. Many investigators now favour the newer approach, where fewer minor symptoms are needed to establish the diagnosis.[42]

Use of the looser definition of CFS has led to an apparent increase in prevalence of the disorder.[43] In a series of 94 patients with suspected CFS, 48 met the 1988 CDC definition, a further 20 met the 1994 definition, but 26 met neither criterion.[44] The 1994 CDC criteria seem more likely to include male, married and high-school educated cases, but a smaller proportion of those diagnosed have the acute onset of signs and symptoms suggestive of an infectious process.[44]

1.2 Prevalence of Chronic Fatigue Syndrome (CFS)

Prevalence of CFS has most commonly been related to samples of patients complaining of fatigue; for example, in a Japanese general population sample of 137 cases of fatigue, 2 individuals met the British criteria of CFS, so that point and 9-month prevalence rates of 1.5% (0.4 to 5.2%) were estimated.[45] Likewise, a cross-sectional telephone survey of 16 970 San Francisco residents, supplemented by detailed interviews of those with symptoms of fatigue, found 1.8% of idiopathic chronic fatigue–like cases, but only 0.2% of CFS-like cases.[46,47] A review of patients under the age of 40 years found that of 297 individuals with fatigue, 3 had CFS and 64 had unexplained chronic fatigue;

various criteria of CFS were more common in those with chronic fatigue than in the remaining 230 patients.[48] Likewise, a study from Hong Kong found that only 3% of those patients with fatigue of more than 6 months duration had CFS.[49] These studies illustrate that if standard criteria of CFS are applied, very few of those in the general population who complain of chronic fatigue have CFS. Comparable figures do not appear to be available for athletes, but we may anticipate at least as large a gap between the prevalence of fatigue and of CFS.

Particularly in the US, the apparent prevalence of CFS seems to be influenced by access to medical care, although other factors may include gender and ethnic group differences in the response to various symptoms. Medical examination of potential cases identified by random telephone interviews suggested an overall population prevalence of about 0.4%, with a disproportionate number of cases among women, minority groups and those of low socioeconomic status.[50]

Using the 1988 definition, a review of 600 cases of depression taken from 23 000 Dutch patients seen in general practice or primary healthcare centres suggested a CFS prevalence of 0.11%, with a male:female ratio of 1:5.[51] Circulation of a questionnaire to 6657 Dutch general practitioners (response rate 60%) confirmed an overall CFS prevalence of 0.11%, with primary fibromyalgia in a further 0.16% of patients; 81% of the CFS cases were women.[52] Responses from 118 of 200 Irish general practitioners likewise suggested a prevalence of 0.1%, with a male:female ratio of 1:2,[34] and one report set the overall US population prevalence as low as 8.7 per 100 000 people.[53]

In nurses (faced by the combined stresses of shift work, heavy lifting and a potential high rate of exposure to viruses), the prevalence of CFS was estimated at 1.09%.[54] In Britain, a case-control study of 2376 individuals aged 18 to 45 years found a point CFS prevalence of 2.6%, falling to 0.5% when comorbid psychological disorders were excluded; in this study, there was a modest predominance in females, but no effect of social class.[55]

2. Functional Characteristics

2.1 Habitual Physical Activity

Athletes with overtraining and/or CFS are usually advised to restrict their daily activity, as are nonathletes who develop CFS. It is thus unclear how far changes in functional characteristics are a primary consequence of the syndrome, and how far they are caused by secondary deconditioning. Use of structural equation modelling suggests that there is often a vicious cycle of inactivity. The attribution of complaints to a somatic cause induces a low level of habitual physical activity, and this in turn increases the severity of fatigue.[56]

Self-reports and actometer data show that habitual levels of physical activity among people with CFS are generally lower than in the general population,[56,57] irrespective of the medical advice that has been given, and there is a desire to avoid activities which the patient believes will cause fatigue.[57] However, the extent of disability and the decrease in habitual physical activity are not always as great as is suggested by subjective reports.[57-59] Indeed, Mullis et al.[59] saw no exacerbation of symptoms in 97% of patients after maximal exercise testing. Low levels of physical activity seem particularly likely if complaints are attributed to a somatic cause, and the reduced physical activity in turn exacerbates the severity of fatigue.[56] Sisto et al.[60] further noted that in the 2 weeks following performance of a maximal treadmill test, there was a significant decrease in average activity and an increased tendency to take rests when exercising. Nevertheless, patients seem more aware of their levels of physical activity than in other disabling conditions such as multiple sclerosis, and often there is a deliberate avoidance of tasks that the patient anticipates will cause fatigue.[57]

2.2 Evidence of Deconditioning

Muscle strength may be normal in CFS.[61,62] However, there is evidence of significant aerobic deconditioning. Echocardiography in 273 cases of CFS revealed smaller left ventricular end-systolic

and end-diastolic volumes, and a decrease of left ventricular mass relative to anticipated normal values.[63] There were also decreases in high density lipoprotein (HDL)-cholesterol and the HDL-total cholesterol ratio, and an increase in the percentage of body fat as assessed by dual energy x-ray absorptiometry.[63]

2.3 Performance of Submaximal Exercise

Moderate exercise can often be performed without exacerbating symptoms, and sometimes it leads to an improvement of the immediate condition.

Nine women and one man with CFS performed ten 3-minute intermittent periods of treadmill walking at a self-selected pace, with no change of condition over the following 7 days.[58] Nevertheless, when questioned, all 10 patients thought that they would be unable to exercise continuously for 30 minutes without exacerbating their symptoms. Peterson et al.[64] found that 30 minutes of walking at 1.6 km/h worsened both fatigue and muscle weakness over the next 40 minutes. Komaroff and Buchwald[3] also noted a worsening of cognition in 70% of individuals with CFS, after exertion. In contrast, Lloyd et al.[65] reported that repetition of a submaximal handgrip exercise for 30 minutes decreased fatigue, depression and confusion.

The relationship of oxygen intake to power output is much the same as in healthy adults, suggesting a normal mechanical efficiency of effort.[59] Nevertheless, one report has described abnormalities of gait in 12 individuals with CFS,[66] possibly secondary to deconditioning or fatigue. Measurements of cortical function showed reduced premovement potentials and a slowing of reaction times for both a target detection and a short term memory task.[67] Studies of cognition are complicated by the impact of depression and subjective impressions of fatigue upon test scores;[68] they may show no change[69] or a worsening of function,[3,68] possibly depending on the intensity of effort relative to the individual's current physical condition.

Block et al.[70] found low resting values of phosphocreatine, but normal rates of recovery following calf muscle exercise. In contrast, near infrared spectroscopic examination of oxygen-haem resaturation and magnetic resonance spectroscopic evaluation of phosphocreatine resynthesis sometimes showed a reduction of oxygen delivery and a slowing of recovery processes in the exercising muscles of patients with CFS.[71] Some cases of CFS also show impaired mitochondrial oxidative phosphorylation, with a plasma accumulation of lactate below the anaerobic threshold,[72] and an associated decrease in the proportion of type I muscle fibres[73] (which might compromise endurance performance). However, it is less clear whether local changes in blood flow and muscle metabolism are specific manifestations of the disease, or a consequence of restricted activity levels and resultant muscle wasting.

2.4 Performance of Maximal Exercise

Patients with CFS can perform a progressive cycle ergometer test to exhaustion. Mullis et al.[59] found no exacerbation of symptoms from use of this procedure in 126 of 130 patients. However, Sisto et al.[74] reported that a maximal test exacerbated symptom reports for 7 days, and Blackwood et al.[75] observed that both focused and sustained attention were depressed more than in healthy controls. Scores for the Symbol Digit Modalities Test, the Stroop Word Test and the Stroop Color Test suggested some impairment of cognitive processing both immediately and 24 hours after maximal treadmill exercise.[68] Furthermore, accelerometer measurements demonstrated a significant reduction in spontaneous physical activity 5 to 7 days following the performance of a maximal treadmill test.[60]

The peak oxygen intake is sometimes unaffected by CFS.[69] Sisto et al.[74] found that patients with CFS could attain 98% of the age-predicted treadmill maximal oxygen intake. However, the case history of an elite ultra-endurance cyclist showed an 8% deterioration in peak power output, a 13% decrease in peak oxygen intake and a 14% decrease in anaerobic threshold associated with the development of CFS. A second test after the athlete had shown substantial symptomatic improvement

showed further decreases in all 3 variables (8%, 10% and 8%, respectively).[11] This supports the view that the deterioration in function is (at least in part) a secondary consequence of restricted physical activity.

A further factor in many patients with CFS is a deliberate limitation of peak effort. Thus, Fischler et al.[76] noted that many cases failed to achieve 85% of their age-predicted maximal heart rate during a progressive exercise test. Ratings of perceived effort and fatigue during treadmill testing were also greater than in healthy adults.[75] Furthermore, there seems to be an association between such indices of 'effort avoidance' and functional impairment.[76]

3. Personality, Affect and Cognitive Function

3.1 Personality

There have been suggestions that a particular type of personality is vulnerable to CFS. In the case of athletes, some individuals are more discouraged than others by development of a minor infection or observation of a small decrement in their current performance. Nevertheless, the nature of the vulnerable personality remains to be defined clearly.

There have been suggestions that those affected by CFS tend to be perfectionists. However, a comparison of 101 cases of CFS with 45 cases of rheumatoid arthritis,[77] and a second comparison between 40 cases of CFS and 31 normal individuals[78] each failed to confirm the perfectionist stereotype, with negative attitudes towards psychiatry.[77]

High scores on neuroticism and low scores on extraversion were found mainly during periods when patients were ill, suggesting these findings were a reaction to CFS rather than precipitating factors.[79]

Christodoulou et al.[80] found elevated levels of Harm Avoidance, and reduced levels of Reward Dependence in individuals with CFS. A good outcome is associated with a change in avoidance behaviour, particularly a change in beliefs about avoidance of exercise and other types of activity.[81] Interventions should thus seek to discourage avoidance of activity and increase perceived control over health.[82]

3.2 Affect

The appreciation of fatigue is so clearly linked to mood state that it is hardly surprising a high proportion of patients with CFS are also severely depressed. In the general population, depression reduces physical activity, and this exacerbates fatigue and further depresses mood. Likewise, in the competitive athlete a vicious cycle links a depressed mood state and performance. However, it is less clear which of these factors is cause, and which effect.

Brunello et al.[83] noted a substantial overlap between CFS and dysthymia, a prevalent form of subthreshold depression associated with a low drive and thus a low level of physical activity. A low level of self-efficacy is a significant predictor of symptoms in CFS.[84] Depression seems particularly common when the CFS is of gradual rather than of sudden onset,[85] pointing to a possible distinction between cases originating in a psychological disturbance and those with an external trigger such as excessive effort or infection. Morriss et al.[86] found that 42 of 119 individuals with CFS had depression meeting the criteria of the American Psychological Association Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R).[87] Likewise, Fischler and associates[88] noted a high prevalence of generalised anxiety disorder in CFS, and a survey of 25 children and adolescents with CFS found that half had psychiatric disorders, mainly anxiety and/or depression.[89] In at least a subgroup of CFS patients, there is a seasonal variation in the extent of depression, much as in seasonal affective disorder.[90]

Although depression could trigger the onset of CFS in some individuals, it is also possible for CFS to develop in the absence of depression.[91,92] Likewise, depression can exist without CFS, as defined by CDC criteria.

3.3 External Stressors

A comparison of 46 individuals with CFS with 46 matched controls suggested that the prevalence of negative life events was 1.9 times the level found in controls during the quarter of the year preceding the illness.[93] This suggests that the negative events may have been a triggering factor in at least a proportion of cases of CFS (although CFS could also precipitate some negative events, or exacerbate the perception of such events).

3.4 Mental Processing

Both CFS and depression are associated with a slowing of average mental processing and reaction speeds.[94] A comparison of 36 individuals with CFS who had no detectable psychiatric comorbidity with 31 healthy controls found deficits of memory, attention and information processing in CFS.[95] Deficits of memory, attention and concentration were related to functional impairment, even after partialling out the contribution of depressive symptomatology.[96] A comparison of 67 individuals with CFS with 126 normal individuals also showed a more rapid development of mental fatigue in CFS.[97] However, focused attention (the ability to attend to a task while ignoring irrelevant stimuli) was unimpaired.[98]

Delayed acquisition of a classically conditioned eye-blink response points to an associative deficit.[99] Averaged data showed a slowing of complex information processing speed and efficiency in CFS,[100] with poor scores on tests in which motor and cognitive processing speeds are critical factors (e.g. reaction time tasks).[69]

Analysis by individual cases revealed that only a minority of individuals have a significant slowing of mental processing and a slow motor speed.[101] Furthermore, patient reports of cognitive difficulties (attention, concentration, memory and reasoning) usually exceeded the findings in objective tests.[99,102,103] Part of the problem may be the artificial nature of laboratory tests, and Wearden and Appleby[103] were able to demonstrate difficulty in the recall of a text in patients with CFS and depression. The deterioration in mental processing appears related in part to a low level of physical activity,[101] and some observers have suggested that it might be a secondary effect of lack of arousal. However, a comparison of 29 cases of CFS with 22 healthy controls found attentional dysfunction, a poor initial storage of information and a reduced processing speed and efficiency, despite a normal level of arousal.[104] Possibly, effects of the anxiety and depression associated with CFS are not completely eliminated by the statistical techniques of 'partialling out' depressive symptomatology.[96]

4. Autonomic Dysfunction

4.1 General Considerations

Overtraining has been associated with 2 types of autonomic dysfunction;[8,105-107] the sympathetic type may reflect an adaptive stress response, and the parasympathetic form is associated with exhaustion of the neuro-endocrine system. As might be anticipated from this, autonomic dysfunction in CFS is generally manifested as a suppression of parasympathetic function and the development of exertional hypotension. As with so many other expressions of CFS, a post-viral neuropathy could be one precipitating factor, but many of the observed changes in both athletes and nonathletes are likely to be a secondary consequence of decreased physical activity and resultant deconditioning.[108,109]

4.2 Parasympathetic Suppression

Some investigators have found relatively normal autonomic and cardiovascular function in CFS. For example, a comparison of 37 patients with CFS with 38 healthy controls found no gross alterations in autonomic function.[110] At rest, both blood pressures and heart rates were comparable for the 2 groups, and both showed a similar increase of heart rate in response to standing. However, the heart rate increase during mental arithmetic was less in those with CFS (23 *vs* 30 beats/min). This could not be explained simply by a lesser degree of concentration in the patients with CFS, and it suggests that their cardiac responsiveness to sympathetic

stimulation was reduced relative to normal controls[110] – a somewhat surprising finding, since reduced reactivity is normally associated with physical conditioning.[111]

One spectral analysis of R-R intervals and systolic arterial blood pressure variability suggested that as in an anxiety state, CFS is characterised by a prevailing sympathetic modulation of the sinoatrial node at rest, but with a reduced response to excitatory stimuli.[54] A comparison of 23 individuals with CFS versus controls found significant increases in both baseline heart rate and the response to standing or tilting.[108] Measures of heart rate variability showed a suppression of parasympathetic function, and in 6 of the 23 individuals with CFS there was a positive tilt table test. Nevertheless, such findings could be a secondary consequence of deconditioning, since the magnitude of changes was significantly correlated with current levels of physical activity.[108] A comparison of 21 patients with CFS (1988 CDC criteria) with 13 age- and gender-matched controls also found that in CFS there was greater than normal sympathetic activity, as assessed by heart rate variability, and higher heart rate responses to tilting (89 *vs* 78 beats/min).[112] Spectral indices of BP variability in the supine position (but not when standing) were also lower in CFS, again indicating an autonomic shift towards sympathetic dominance.[113] However, a fourth analysis found no differences of heart rate variability between 19 adults with CFS as defined by CDC and 11 controls, either in the supine position or on tilting to the vertical position.[114]

Given the major influence of training on cardiac performance and peripheral venous tone, the rest or reduced training commonly recommended for patients with CFS could in itself predispose to a shift in sympathetic/parasympathetic balance and susceptibility to orthostatic hypotension.

4.3 Orthostatic Hypotension

A low blood pressure has been noted as one feature of the parasympathetic form of overtraining.[105] Fatigue is also a commonly reported symptom in patients with orthostatic hypotension.[115] Some authors have thus suggested that autonomic disturbances may play a role in the onset of CFS,[116] through a neurally-mediated hypotension[117,118] and other disturbances in the HPA axis.[119-121] Such an hypothesis suggests a potential for the treatment of CFS with a combination of positive inotropic drugs[117] and graded exercise. Another group of investigators has identified a subset of CFS patients with Ehlers-Danlos syndrome;[122] the abnormal connective tissue in the dependent blood vessels of individuals affected by this condition predisposes to orthostatic hypotension.

A Dutch study[123] noted an increase in the circadian rhythm of blood pressure in 18 individuals with CFS relative to 12 normotensive controls. In the cases of CFS, night-time systolic pressures were consistently less than 100mm Hg.[123] A pilot trial involving 4 individuals suggested that the low night-time pressures could be alleviated by administering inopamil (200 mg/day).[123]

Many observers have found abnormal tilt-table responses in a proportion of CFS cases. In a study[124] of adolescents, head-up tilt induced vasovagal faints in 4 out of 13 apparently healthy individuals; all 25 individuals with CFS showed severe orthostatic symptoms, although only 2 out of 25 developed syncope.[124] Acrocyanosis, cool extremities and oedema suggested venous pooling in 18 of the 25 patients.[125] A comparison of adults with CFS versus physically inactive normal controls noted positive tilt tests (here defined as a drop in systolic blood pressure >25mm Hg, with no concurrent increase in heart rate, and/or presyncopal symptoms) in 11 of the 39 individuals with CFS and 12 of the 31 healthy individuals. However, those with CFS had higher heart rates and smaller cardiac stroke volumes, as assessed by impedance cardiography.[126] Schondorf and associates[127] had similar findings, head-up tilt causing syncope in 16 of the 75 individuals with CFS and 8 of the 48 controls. A more substantial survey compared 78 patients meeting CDC criteria of CFS with 38 healthy controls; this showed that 22 of the 78 individuals with CFS manifested hypotension on up-

right tilt.[128] After 8 weeks of sodium ion therapy (1200 mg/day), hypotension was corrected in 11 of the 22 patients, with a reduction in symptoms. The remaining 11 patients showed a significant reduction in plasma renin activity (0.79 *vs* normal 1.29 pmol/ml/h).[128]

Office and 24-hour ambulatory blood pressure recordings showed no decrease in resting, nighttime or 24-hour readings in 38 CFS patients relative to 38 age-matched controls.[113] Nevertheless, resting heart rates were consistently higher in patients with CFS, both in the office (77 *vs* 68 beats/min) and when averaged over 24 hours (77 *vs* 67 beats/min).

We may conclude that autonomic dysfunction could trigger CFS in a proportion of cases. In athletes, one possible exacerbating factor could be the hypotension associated with progressive salt depletion when undergoing prolonged and rigorous training in a hot environment.[129]

Table II. Hormonal factors suggested as influencing chronic fatigue syndrome

Excess of arginine vasopressin[130]
Dysfunction of hypothalamic-pituitary-adrenal axis[131]
Blunted release of corticotropin (ACTH) and cortisol
to corticorelin (corticotropin-releasing hormone; CRH)[132]
to naloxone[133]
to ipsapirone[134]
Cortisol
low resting[135]
high resting[136]
Small adrenal glands[137]
Low melatonin[138]
Excess of serotonin (5-hydroxytryptamine; 5-HT)[120,134,138]
Androgens
low resting[139,140]
blunted release to corticotropin[141]
Low estrogens[142,143]
Somatomedin 1
increased[144]
decreased[145]

5. Hormonal Influences

5.1 General Considerations

Given the close connection between the neurohypophysis and the pituitary-adrenal axis, hormonal manifestations of any disturbance in mood state are to be anticipated in CFS. In practice, a variety of hormonal disturbances have been suggested and/or detected in individuals with CFS, offering the potential prospect of treatment by administration of appropriate agonists or antagonists (table II).

5.2 Serotonin, Corticotropin and Cortisol

According to the classical theory of Selye,[146] a moderate level of stress enhances adrenal function, but hypoactivity and even atrophy of the adrenal gland are common manifestations of excessive physical and/or psychological stress. Some authors have further suggested that body reactions depend on the source of stress (physical effort, anxiety or depression), the options available to alleviate the situation, and the individual's appraisal of their ability to meet the challenge.[147]

An excessive perceived stress contributes to the sensation of fatigue, and has been described commonly among individuals experiencing both overtraining[148] and CFS.[131] The basis of any associated dysfunction of the HPA axis in CFS is unclear. Some recent data suggest a disturbance of serotonergic neurotransmission, with alterations in the neurally-induced activity of arginine vasopressin, an important co-secretagogue that influences function of the HPA axis in conjunction with corticorelin (corticotropin-releasing hormone; CRH).[120,121,134] In some instances, an autoimmune pathology may be involved;[138] this, also, has been associated with increased levels of serotonin (5-hydroxytryptamine; 5-HT) and decreased levels of melatonin.[138]

Cortisol levels in athletes with CFS tend to be high relative to those levels in their peers who have trained to the point where their competitive performance and mood state are beginning to deteriorate.[149] Cortisol readings for those who have developed CFS are inconsistent, perhaps because individual samples are generally small, reactions to stress differ from one person to another, and CFS has a multifaceted aetiology. Scott and Dinan observed significantly lower levels of urinary free

cortisol in 21 patients with CFS than in 15 healthy controls.[150] In contrast, Young et al. found no difference in basal values for salivary and urinary cortisol between 22 cases of CFS and appropriate controls.[151] Likewise, basal corticotropin and cortisol levels were comparable in 14 individuals with CDC-diagnosed CFS and 14 healthy volunteers, although there was a significant blunting in the release of both corticotropin and cortisol in response to administration of a 100mg dose of corticorelin,[132] the opioid antagonist naloxone,[133] or 20mg of the serotoninergic agonist ipsapirone.[134]

MacHale and associates[152] found a suppression of the normal diurnal rhythm of cortisol levels in 15 individuals with CFS; thus morning values tended to be low and evening values high relative to age- and gender-matched controls. A second study[153] found a normal circadian profile of serum cortisol. A further analysis of salivary cortisol found low evening and (in those individuals without concomitant psychiatric disorders) low morning values relative to controls, with an overall hyposecretion of cortisol.[135] Another group collected 16 hourly samples of saliva, finding significantly greater average cortisol levels in 10 individuals with CFS than in 10 healthy volunteers.[136]

Eight individuals with CFS and a subnormal response to corticotropin stimulation underwent computer tomography. In these individuals, the size of the adrenal gland was only 50% of that found in 55 healthy individuals.[137] Perhaps because of a reduced cortisol production, the dose of dexamethasone needed to induce a 50% inhibition of interleukin (IL)-4 production and CD4+ cell proliferation was 10 to 20 times lower in individuals with CFS than in normal individuals.

In a series of 32 cases meeting strict diagnostic criteria for CFS, without comorbid psychiatric disorders, 1 month of low dose hydrocortisone (5 or 10mg daily) yielded a significant reduction in self-reported fatigue relative to treatment of the same patients by placebo; 9 of 32 patients reached a normal range on the fatigue scale.[154] McKenzie et al.[155] also noted that relative to randomised placebo controls there was some improvement of CFS symptoms in those receiving low dose oral hydrocortisone (16 mg/m^2 per day for 12 weeks); however, the extent of adrenal suppression induced by cortisone was such that it could not be recommended as a practical treatment for CFS.[155]

5.3 Dehydroepiandrosterone and Estrogens

Overtraining is well-recognised as causing a temporary suppression of androgen and estrogen secretion,[156] with a decrease in the ratio of anabolic to catabolic hormones.[157,158] For an athlete, a situation could thus be reached where the tissues are unable to recover from training, continuing to break down rather than develop a positive adaptation. The depression of gonadal hormone production could also contribute to both immunological disturbances and overall symptomatology.[141] Dehydroepiandrosterone (DHEA; prasterone) levels are reputed to influence sleep, memory, stress, anxiety and depression.[139]

The contribution of gonadal disturbances to CFS may extend beyond competitive athletes, since Harlow and associates[142] reported that 150 women meeting the 1988 CDC criteria for CFS were more susceptible to irregular menstrual cycles and amenorrhoea than 149 healthy controls. A history of abnormal ovarian function, including ovarian cysts, hirsutism and frequent anovulatory cycles suggested the development of ovarian hyperandrogenism or hyperprolactinaemia.[142] Further, a study of patients with CFS reported that although basal DHEA levels were normal, affected individuals showed a blunted response to adrenal stimulation by corticotropin.[141] Other reports found reduced basal levels of DHEA and its sulphate derivative in 15 individuals with CFS, relative to 11 healthy individuals;[140] and low levels of DHEA in 'the majority of Japanese patients with CFS'.[139]

Some recent work suggests that estrogen therapy can enhance mood state in women with CFS.[143] However, it is unlikely that the use of anabolic agents would be sanctioned for the treatment of CFS in competitive athletes.

5.4 Arginine Vasopressin

The pituitary release of antidiuretic hormone normally increases as a function of exercise intensity, with further secretion induced by the fall in blood volume and increased plasma osmolality of prolonged physical activity.[159] However, regulatory mechanisms could be disrupted as a consequence of exercise or stress-induced hypophyseal dysfunction, and an excessive or a deficient release of vasopressin.

Some of the symptoms of CFS, including mental confusion, exertional malaise, changes in body mass and joint pains are also seen in the syndrome of serum inappropriate anti-diuretic hormone.[130] Moreover, both syndromes can be triggered by physical exertion, emotional stress, hypotension and a viral illness. It has thus been suggested that an inappropriate release or sensitivity to arginine vasopressin could be one further factor contributing to CFS, with a potential for treatment of such cases by salt loading and/or a direct inhibition of arginine vasopressin.[130]

5.5 Melatonin

Melatonin is derived from serotonin, and thus from tryptophan. It is associated with the nocturnal depression of arousal, but also increases the sense of well-being,[160] and perhaps for this reason it has sometimes been prescribed for patients with CFS. Reduced levels of melatonin have been described in cases of CFS associated with autoimmune thyroiditis.[138] However, in most instances there seems little basis for such treatment, since melatonin levels are generally normal in individuals with CFS, with no evidence of disruption of diurnal rhythms.[161]

5.6 Growth Hormone and Somatomedin 1

Heavy athletic training is associated with an increased release of growth hormone relative to cortisol, possibly in an attempt to maintain the balance between anabolism and catabolism.[107] One recent report suggested that basal levels of somatomedin 1 (insulin-like growth factor 1; IGF) were greater than normal in individuals with CFS, in contrast to fibromyalgia (where subnormal values were observed).[144] However, Allain et al.[145] found attenuated basal levels of both somatomedin 1 and somatomedin 2 in individuals with CFS, with a reduced growth hormone response to hypoglycaemia. The latter authors cautioned that it was unclear whether their findings were the consequence of a primary pathological process, or a secondary response to a reduction in habitual physical activity.

6. Nutritional Influences

6.1 General Considerations

Repeated bouts of prolonged exercise, heavy sweating, illness and an inadequate or poorly balanced diet can all contribute to depletion of nutritional reserves, with cumulative fatigue and immunosuppression. Potential deficiencies encompass various B vitamins, ascorbic acid (vitamin C), magnesium, sodium, zinc, phosphate, monosaccharides, tryptophan, carnitine, glutathione, coenzyme Q10 and essential fatty acids;[130,162-168] (table III).

In uncontrolled experiments, such as a trial which suggested that CFS patients benefited from a 9-month intake of freeze-dried aloes,[174] a placebo effect could also be involved. However, there are good reasons to suppose that deficiencies in many of the other nutritional constituents could affect both performance and perceptions of fatigue.

6.2 B Vitamins

Requirements of the B-group vitamins depend upon the individual's cumulative weekly energy expenditure. Given an adequate mixed diet, there is no fundamental reason why those performing heavy endurance training should develop a deficiency, although a survey of Dutch endurance cyclists suggested a low intake of thiamine (vitamin B1) and pyridoxine (vitamin B6).[175] Moreover, patients with CFS sometimes reported benefit from taking B-group vitamins, and one assessment of vitamin-dependent enzymes (aspartate aminotransferase for pyridoxine, glutathione reductase

Table III. Nutritional deficits suggested as contributing to chronic fatigue syndrome

B vitamins[165,169]
Inorganic elements
sodium[128]
magnesium[164]
phosphorus[163]
Amino acids
carnitine[170]
glutathione[162]
tryptophan[171,172]
Monosaccharides[166]
Essential fatty acids[173]

for riboflavin, and transketolase for thiamine) found lower activities in 12 vitamin-untreated patients with CFS than in 18 healthy age and gender-matched controls.[165]

Regland et al.[169] found increased levels of homocysteine in the cerebrospinal fluid in individuals with CFS; these were associated with fatigability and a low level of cyanocobalamin (vitamin B12), which plays an important role in the remethylation of homocysteine.

6.3 Sodium

Sodium depletion may arise in conjunction with alterations in water balance secondary to an excessive release of arginine vasopressin or an inadequate secretion of renin (see section 5.4). Repeated bouts of prolonged exercise in the heat can also give rise to cumulative sodium depletion, with an associated decrease of body mass, hypotension and fatigue.[129]

One group of investigators isolated a subgroup of patients with CFS where symptoms were reduced by 8 weeks of additional sodium (1200 mg/day).[128]

6.4 Magnesium

Magnesium levels influence the ratio of ATP to ADP and thus the ability of muscle to contract.[129] Low serum magnesium levels can arise in gymnasts and distance runners who deliberately restrict food intake, or consume an unbalanced diet with a high carbohydrate and fibre content.[175-178] A cumulative depletion of magnesium reserves may also develop with repeated bouts of endurance exercise in the heat.[129] A magnesium deficit could thus contribute to both the neurocirculatory asthenia and other symptoms of CFS.[164] As yet, there do not seem to have been any trials of magnesium therapy in CFS.

6.5 Phosphate

The term 'phosphate diabetes' has been applied to a deficient reabsorption of phosphate in the proximal renal tubules. The resultant loss of buffering capacity inhibits both aerobic and anaerobic metabolism, giving rise to symptoms of myalgia, fatigue and mild depression.[163] An examination of phosphate reabsorption in the proximal renal tubules, phosphate clearance and the renal threshold for phosphate suggested that 9 out of 87 patients with CFS had the metabolic characteristics anticipated in phosphate diabetes.[163]

The anxiety associated with chronic fatigue, exposure to various types of stress, and (in the athlete) a deterioration in competitive performance could contribute to hyperventilation and a systematic depletion of blood buffering capacity mirroring that seen in phosphate diabetes.

6.6 Monosaccharides

Glycogen depletion is an immediate cause of fatigue. The resulting depletion of blood glucose levels leads to depletion of plasma amino acids, possibly predisposing to immunosuppression and exercise-induced infection.[179] Mobilisation of free fatty acids and a decrease in blood levels of branch-chained amino-acids (BCAA) also increase the transport of tryptophan into the brain (see section 6.7).[180]

The decrease in BCAA could be countered either by administering carbohydrate or BCAA supplements. In accordance with this expectation, some studies of athletes have found carbohydrate supplements alone are an effective tactic to delay central fatigue,[181,182] and others have found benefit from BCAA.[171,180,183] It is less clear why

monosaccharides should be depleted in the general population. Nevertheless, a glyconutrient preparation providing the 8 monosaccharides needed to synthesise glycoproteins apparently reduced *in vitro* immunological changes in CFS (see section 7.3).[166]

6.7 Tryptophan

Tryptophan is the precursor of the neurotransmitter 5-hydroxytryptamine (serotonin), involved in fatigue and sleep. It has been taken by some athletes as a means of increasing growth hormone secretion,[184] and its administration in North America is now banned because of a suspicion of its association with the eosinophilia-myalgia syndrome.[185]

The passage of tryptophan across the blood/brain barrier depends on the plasma free tryptophan level, and thus the ratio of tryptophan to BCAA.[172] Metabolism of BCAA during prolonged, heavy endurance exercise would be expected to increase free tryptophan levels and thus fatigue. CFS patients show increased resting levels of free tryptophan, but (perhaps because they are unable to undertake very heavy exercise), free tryptophan levels in such individuals are not increased by exercise.[172] On the other hand, the ingestion of BCAA can reduce ratings of perceived exertion and fatigue in healthy athletes when a test bout of exercise follows a previous evening of glycogen-depleting endurance effort.[171,180,183]

6.8 Carnitine

Carnitine plays a role in the transport of long-chained fatty acids across the mitochondrial membrane, and is also implicated in the metabolism of BCAA. It could thus influence 5-hydroxytryptamine levels (section 6.7). Low levels of serum acyl carnitine have been observed in both Japanese and Swedish patients with CFS, although the practical importance of this finding is unclear, given that there are also large differences in serum acyl carnitine levels between healthy Swedish and Japanese individuals,[170] with as yet no evidence of differences in the prevalence of CFS.

6.9 Glutamine

It has been suggested that prolonged endurance exercise can impair immune function by depleting plasma glutamine reserves;[179] this in turn could precipitate or activate a viral infection, providing one mechanism for development of CFS. Further, a combination of prolonged endurance exercise and chronic infection might exacerbate glutamine depletion, to the point where the function of both skeletal muscle and the central nervous system were threatened not only by a lack of carbohydrate, but also by a fatiguing lack of all potential aerobic metabolites.[162]

A small reduction of plasma glutamine is seen with prolonged endurance exercise,[186] but its practical importance is doubtful, since glutamine supplements do not normally reverse the exercise-induced immunosuppression.[187]

6.10 Essential Fatty Acids

In athletes, reliance on a high carbohydrate diet increases glycogen reserves, but it has the disadvantage of reducing the ability to metabolise fat, which is important once prolonged exercise has depleted the carbohydrate stores.

In a double-blind, placebo-controlled trial involving 63 adults with chronic severe fatigue, myalgia and various psychiatric symptoms, Behan et al.[173] found benefit from high doses of essential fatty acids (8×500mg capsules per day of linoleic, γ-linoleic, eicosapentaenoic and docosahexaenoic acids). At 3 months, 85% of the test group and only 17% of the control group reported an alleviation of symptoms. Moreover, low initial levels of essential fatty acids in the red cell membranes were corrected by the dietary supplement.

However, the mechanism of benefit remains unclear, and Warren et al.[167] were unable to replicate these findings in a case-controlled study of 50 patients meeting the more precise Oxford Criteria for CFS. In their study, pre-treatment red cell levels of essential fatty acids were normal, and 3 months of the dietary supplement gave no symptomatic improvement over controls.

7. Immune Function

7.1 General Considerations

A disturbance of immune function sufficient to increase the risk of clinical infection is a common expression of overtraining in athletes.[8,188-191] Given the close interaction between the HPA axis and the immune system, a disturbance of immune function also seems likely in individuals with CFS. If immune dysfunction is indeed a dominant component of CFS, then it could shade imperceptibly into the overtraining syndrome among active individuals. In support of this view, a patient who appears to be recovering from CFS may show a severe relapse a few hours to 2 days following an acute bout of physical activity.[192,193]

Hypoxia suppresses T cell–mediated immune function,[194] perhaps through an increased production of endogenous glucocorticoids, or perhaps by exacerbating the normal exercise-related decrease in plasma glutamine levels.[9] Thus, problems are particularly likely to be observed in athletes undergoing heavy training at real or simulated altitude.[9] Other forms of stress (both psychological and environmental) are also likely to exacerbate immunosuppression for many athletes.[195]

Formal measures of immune function in CFS are inconsistent, with most case series failing to show one or more of the reported disturbances in the immune response (table IV). Indeed, one case-control series rigidly adhering to the CDC definition of CFS found only marginal changes in cytokines and cell surface markers, and no changes in immune complex, complement or serum immunoglobulin (Ig) levels, natural killer (NK) cell function or proliferative responses to mitogens and antigens.[212] However, other reports of immune disturbances are sufficiently frequent to merit detailed discussion.

Table IV. Immunological changes in chronic fatigue syndrome

Cell counts
increased percentage CD8+ cells[196]
increased NK cell count[196]
Cell characteristics
changes in T cell proliferation[197,198]
activation of CD8+ cells[199]
reduction of NK cell activity[166,200,201]
dysfunction of nitric oxide-mediated NK cell activation[202]
reduced expression of CD5, CD8, CD11a[166]
increased expression of class II antigens[203]
reduced expression of CD28
increased apoptosis[166]
Ig and antibodies
decreases in IgG_1 and IgG_3 [204]
increase in auto-antibodies[138,205]
Other soluble factors
increased IL-1ra secretion[206]
increased basal levels of IL-6[207,208]
increased production of TNFα[208,209]
reduced production of IFNγ[197]
decreased production of IL-10[208]
increased C-reactive protein[210]
increased β2-microglobulin[210]
increased neopterin[210]
increased TGFβ[211]

IFNγ = interferon-γ; **Ig** = immunoglobulin; **IL** = interleukin; **IL-1ra** = interleukin-1 receptor antagonist; **NK** = natural killer; **TGF**β = transforming growth factor-β; **TNF**α = tumour necrosis factor-α.

7.2 Cell Counts

Changes in cell count in CFS are not very striking. A case-control series showed no changes in resting leucocyte numbers in individuals with CFS.[212] The counts for total leucocytes, T cells, B cells, NK cells, CD3+, CD4+ and CD8+ cells did not differ between 20 female patients with CFS and 14 matched sedentary controls either before or following exhausting exercise, although the patients demonstrated substantially more fatigue 24 hours after exercise.[213]

Susceptibility to infection reflects a decrease in NK cell counts and/or activity. Such changes are observed in athletes who are undergoing heavy training.[214] However, Peakman et al.[196] noted an increase in NK cell count and the percentage of CD8+ cells in individuals with CFS, with no correlation between cell counts and symptoms, and no changes as clinical condition improved. Likewise, there was no evidence of an excessive neutrophilia following a 15-minute stepping exercise, although in contrast to normal controls, patients with CFS showed no significant correlations between the ex-

tent of neutrophilia and either urinary cortisol or plasma creatine kinase; this may indicate some disturbance in the normal hormonal regulation of cell counts.[215]

A comparison between civilian cases of CFS and cases apparently induced by the stresses of the Gulf War again showed no abnormalities of leucocyte count in the civilians, although veterans with CFS had more total and major histocompatibility complex (MHC II+) T cells and a lower NK cell count than controls.[13]

7.3 Functional Characteristics

Functional characteristics of a number of key leucocyte subsets are adversely affected by very heavy exercise.[214] Patients with CFS also show changes in leucocyte function. Cell surface expression of the glycoproteins CD5, CD8 and CD11a was significantly reduced in individuals with CFS,[166] the last change being important to lymphocyte mobilisation. There was no increase in CD4+ cells expressing the memory phenotype CD45RA+ (as would be anticipated with chronic activation of the immune system by trauma, septic reactions or infection).[196,204] However, there were other changes suggestive of activation, including an increased expression of class II antigens, and a reduced expression of the co-stimulatory receptor CD28.[203] An activation of CD8+ cytotoxic/suppressor cells has also been reported in affected individuals.[199]

Visser et al.[197] found a normal resting proliferation of CD4+ cells in individuals with CFS, but the dose of dexamethasone needed to inhibit proliferation was much reduced.[197] In contrast, Kavelaars et al.[216] observed that the maximal effect of dexamethasone on T cell proliferation was significantly diminished in individuals with CFS. T cell proliferation occurred earlier in patients with CFS, and proliferation was less marked following live polio vaccination.[198]

NK cell function was depressed in individuals with CFS,[166,200,201] implying a reduction of lytic activity per NK cell. In particular, there was a dysfunction of nitric oxide (NO)-mediated NK cell activation in individuals with CFS. The expression of inducible NO synthase transcripts in peripheral blood mononuclear cells did not differ from that seen in normal controls, but addition of arginine failed to enhance NK activity in patients with CFS, and incubation with the NO donor S-nitroso-N-acetyl penicillinamine also failed to enhance NK activity as it would in healthy individuals.[202]

Apoptosis was more frequent in individuals with CFS than in healthy adults,[166] perhaps because of an increase in the interferon (IFN)-induced protein kinase RNA (PKR) and protein.[217] There was also an increased expression of the apoptosis repressor protein bcl-2,[203] and the extent of apoptosis could be reduced as much as 50% by administering 2-aminopurine, a potent inhibitor of PKR.[217] These various changes were reduced when cells were incubated for 48 hours in a medium containing supplements of the 8 monosaccharides critical to the synthesis of glycoproteins.[166]

Both virally- and chemically-induced CFS showed a substantial increase in the IFN-induced proteins 2-5A synthetase and PKR.[218] Lymphocytes showed an associated substantial deficit of the RNAse L inhibitor gene; this could lead to an increased cellular RNA turnover, with a subsequent inhibition of protein synthesis, general fatigue, myalgia and muscle weakness.[219]

The levels of β-endorphin in peripheral blood mononuclear cells were much lower than in healthy controls, possibly reflecting chronic immune activation and a reduction in local stores. Assuming that levels in the central nervous system were similarly reduced, this could account for much of the fatigue and weakness that characterise CFS.[220]

7.4 Cytokines, Lymphocytic Hormones and Other Soluble Factors

A period of very heavy exercise leads to a pro-inflammatory cytokine response similar in pattern if not in extent to that seen in inflammation, sepsis and severe burns.[221] Some of the findings in CFS, such as fatigue, myalgia and low-grade fever, are reminiscent of those associated with infusion of the pro-inflammatory IL-1. However, the findings re-

garding plasma cytokine levels tend to be inconclusive. An assay of messenger RNA (mRNA) for 8 cytokines showed no evidence of activation of the immune system in patients with CFS and secondary depression; indeed, the data suggested a trend to an immunological down-regulation.[222] It has also been hard to demonstrate changes of leucocyte cytokine mRNA in response to exercise[223] and it may be that more attention should be directed to the extra-circulatory production of cytokines, for example by the neuroglial cells.[224] The observed responses in women may also be influenced by the phase of the menstrual cycle; for instance, IL-1 receptor antagonist (IL-1ra) secretion was twice control values during the follicular phase, but was normal during the luteal phase of menstruation.[206] Likewise, IL-1ra secretion was higher in individuals with CFS than in controls during the follicular phase of the menstrual cycle, and IL-2 soluble receptor (IL-sRII) release was greater in both phases of menstruation.[206]

In patients with fatigue following Q fever, aberrant patterns of cytokine release from Q-fever antigen stimulated peripheral blood mononuclear cells have been described, including a decreased production of IL-2 and an increased production of IL-6 and IFNγ,[225] possibly as a consequence of chronic immune stimulation.

7.4.1 Pro-Inflammatory Agents

Significant increases in spontaneous, phytohaemagglutinin (PHA)- and lipopolysaccharide (LPS)-stimulated production of the pro-inflammatory IL-6 were observed in lymphocytes during 'natural fatigue'.[226] Gupta and associates[226] did not observe such changes when fatigue was induced by laboratory exercise, but others have noted such a response with heavy and prolonged exercise.[227] A comparison of 10 patients with CFS with 10 age-, gender- and activity-matched controls showed an increased basal production of IL-6 and higher levels of the acute phase reactant α2-macroglobulin in CFS,[207] possibly suggesting a chronic inflammatory process. However, the IL-6 response to exercise was similar in patients and in controls, and the secretion of IL-Iβ did not differ between groups either at rest or during exercise.[207]

Richardson et al.[228] found that plasma levels of IL-2 and tumour necrosis factor-α (TNFα) were undetectable when individuals with CFS exercised to 70% of their estimated maximal heart rates;[228] they suggested that this was a useful point of distinction from overtraining, where there was a marked secretion of TNFα. However, Moss et al.[209] found support for the hypothesis of an activation of pro-inflammatory mediators, showing increases of serum TNFα in individuals with CFS. Gupta and associates[208] also noted an increased unstimulated production of both IL-6 and TNFα by peripheral blood monocytes (PBMC) in patients with CFS.

Resting CD4+ cells produced less IFNγ in individuals with CFS than in healthy controls,[197] and production of this cytokine was also decreased following live polio vaccination,[198] but plasma IFNγ levels did not differ between individuals with CFS and controls following exhausting exercise.[213]

A comparison of civilian and veteran cases of CFS found that relative to the civilians, the latter group had higher levels of IL-2, IFNγ and TNFα, as well as the anti-inflammatory IL-10.[13]

7.4.2 Anti-Inflammatory Agents

In a healthy adult, the secretion of pro-inflammatory cytokines is quickly followed by the secretion of counter-regulatory, anti-inflammatory agents. In individuals with CFS, the resting IL-4 production was similar to that of controls, but a 10- to 20-fold lesser concentration of dexamethasone was needed to cause a 50% inhibition of IL-4 production in individuals with CFS.[197]

Gupta and associates[208] noted a decreased production of IL-10 in individuals with CFS. Stimulation of IL-10 production and suppression of TNFα production by terbutaline were also attenuated in patients with CFS, suggesting that this disorder is marked by a resistance of the immune system to neuro-endocrine regulation.[216] Veterans with CFS had higher levels of IL-10 than civilians with CFS.[13]

7.4.3 Other Soluble Factors

Relative to controls, patients with CFS have other characteristics suggestive of chronic inflammation, including higher concentrations of C-reactive protein, β2-microglobulin (a constituent of class I MHC proteins), and the growth factors neopterin[210] and transforming growth factor-β.[211]

7.5 Immunoglobulins and Antibodies

A detailed study of circulating immune complexes, and of IgA, IgE, IgG and IgM found only some reduction in levels for 2 subclasses of IgG: IgG_1 and IgG_3.[204] A double-blind trial in 71 adolescents with CFS found benefit from 3 once-monthly infusions of γ-globulin (1g/kg) relative to placebo,[229] but a second double-blind study in 99 adults with CFS found no benefit from treatment at doses varying from 0.5 to 2 g/kg monthly for 3 months.[230]

Fatigue of the CFS type seems common in autoimmune endocrinopathies. In cases of autoimmune thyroiditis, 38 of 118 patients showed symptoms typical of CFS; this was associated with the presence of auto-antibodies against the adrenal glands.[138] Antimuscle and antineural antibodies might also block acetylcholine receptors and calcium channels. Von Mikecz et al.[205] found autoantibodies in 50 of 60 individuals with CFS (83%) compared with only 17% of controls. However, Plioplys[231] was unable to detect any such autoimmune antibodies in patients with CFS.

8. Infection

8.1 General Evidence of Infection in CFS

A period of heavy training is liable to increase an athlete's susceptibility to infection.[188,189,191] It may thus be significant that the onset of CFS in the affected individual is often linked to some type of infection or viral reactivation.

In some of these studies, CFS has not been distinguished clearly from other causes of fatigue. A telephone follow-up of 42 children and adolescents who were enrolled in a chronic fatigue programme found that 60% traced their problem to an acute illness, and 36% reported fever.[232] Random-digit dialling identified Californian adults aged 18 to 60 years with severe fatigue of greater than 1-month duration. After excluding medical and psychiatric conditions, a common feature of the remaining 1510 cases included 'flu-type' symptoms.[34] In one survey of 134 patients with CFS, 72% reported an apparent precipitating infection, although clinical and serological evidence of this was found in only 7% of patients.[14] Another comparison of 46 individuals with CFS versus 46 matched controls reported a prevalence ratio of infections rising from 1.4 to 2.3 anticipated values in the four-quarters preceding the development of CFS.[93] In a third survey, 11 of 23 patients with CFS gave a history of viral infection within the preceding 4 weeks.[108]

On the other hand, 24-hour monitoring of core temperatures by radio-frequency transmitter pills typically showed a normal mean core temperature and a normal circadian rhythm of temperature in patients with CFS.[153] This could be explained if, in some instances, the factor precipitating immune activation was an allergic reaction.[233]

If the perception of a prior illness is correct, there might be a potential for either prevention or treatment by some type of antibacterial or antiviral therapy. Nevertheless, retrospective questioning of those who have developed CFS introduces a risk of recall bias.[234] A further possible issue is an increase of symptom reporting in those susceptible to CFS. A prospective case-control study found a higher incidence of almost all types of disease in individuals who subsequently made an insurance claim for CFS, the highest odds ratio in a multivariate model being for lethargy.[234] Likewise, an analysis of 46 cases of CFS found that there had been a high prevalence of many health problems not only recently, but also over the entire life course. Diagnoses included irritable bowel syndrome, episodes of infectious mononucleosis, herpes infections, allergic rhinitis and asthma.[235]

8.2 Evidence for Epidemics

If there were to be an infectious cause for CFS, epidemics would be anticipated, although an ap-

parent epidemic could also arise through other common features of inheritance or the domestic environment.

Steele et al.[47] found no household clustering of CFS-like cases in 8004 San Francisco households. Likewise, Fukuda et al.[236] were unable to confirm a clustering of cases in 1698 households with cases resembling CFS. Straus concluded:[237] 'There is no credible support for outbreaks or transmission of chronic fatigue syndrome'.

Nevertheless, there are occasional reports of epidemics and familial clustering of CFS.[46,200,238,239] One study noted CDC defined CFS in 5 of 6 siblings and 3 other immediate family members, with a significant depression of NK cell activity; however, 2 of the affected individuals had paediatric malignancies, so that they may have had some genetic abnormality of NK cell function rather than a common source of viral infection.[200] Data from an area of Nevada where there had been an outbreak of unexplained fatiguing illness (including cases of CFS) showed an increased incidence of non-Hodgkin lymphoma and primary brain tumours, but not of lung or breast cancer.[240]

One group of investigators also reported a seasonal distribution of CFS symptom onset,[18] but this could reflect no more than a precipitation of symptoms by seasonal affective disorder. A second investigation found a less than normal seasonal swing of mood state in individuals with CFS.[241] Perhaps the most convincing report of an epidemic concerns an outbreak of neuromyasthenia in New Zealand; in this episode, 23 of the patients were contacted, and of these 10 appeared to meet CDC criteria of CFS, with a further 11 cases having prolonged idiopathic fatigue.[242]

8.3 Responsible Micro-Organisms

Many types of infection are followed by a period of fatigue, but do not necessarily cause the full picture of CFS. Micro-organisms suspected as responsible for episodes of CFS include, among others, the Epstein-Barr and other herpes viruses, enteroviruses, retroviruses,[243] Borna disease virus, poliomyelitis, Q fever, Lyme Borreolis, rubella, brucella and mycoplasmal infections (table V).

8.3.1 Epstein-Barr and Herpes Viruses

The Epstein-Barr virus is carried by 90% of adults in Western Societies, and in at least half of those who are infected it gives rise to no symptoms.[255] The virus becomes incorporated into the DNA of lymphocytes and the epithelial cells of the oropharynx.[256] The micro-organism carries an IL-10 homologue that inhibits B cell expansion, and thus the production of Ig.[257,258] High levels of Epstein-Barr specific T memory cells seem important to the control of infection.[259] Immunosuppression by intensive exercise and/or stress could impair the activity of the specific memory cells, explaining how such an ubiquitous virus could suddenly induce the rare condition of CFS. In support of this hypothesis, there is some evidence that as salivary IgA levels of elite swimmers decrease with heavy training, the Epstein-Barr virus is shed from its normal sites of storage.[260]

Whereas an upper respiratory tract infection (URTI) causes acute fatigue for 2 to 4 weeks, the median duration and interquartile range following a bout of infectious mononucleosis was estimated at 8 (4 to 16) weeks.[261] The relative risks that fatigue would persist for 6 months following an attack of glandular fever and an URTI were 2.7 to 5.1 to 1.[261]

A positive Paul-Bunnell test implies the presence of antibodies which agglutinate and haemolyse

Table V. Micro-organisms associated with chronic fatigue syndrome

Viruses
Epstein-Barr[244]
Herpes virus 6[245,246]
Yersinia enterocolitica[247]
Borna disease[239]
Poliomyelitis[248]
Rubella[249]
Other micro-organisms
Q fever[250]
Lyme borreolis[251]
Brucella[252]
Mycoplasmal infections[253,254]

sheep red cells. It is a relatively specific indicator of infectious mononucleosis, and was described in an elite middle-distance runner who developed infectious mononucleosis during high altitude training.[9] Elevated titres of antibodies to either the Epstein-Barr virus[244] or a related organism (the human herpes virus 6)[245,246] have also been observed in individuals affected by chronic fatigue and/or CFS. However, the viral load generally remains fairly low,[246] and the significance of such observations is questionable, since equivalent titres of the Epstein-Barr virus can also be found in individuals who do not complain of chronic fatigue. A comparison between CDC-defined CFS patients and age-, gender- and race-matched healthy controls showed no significant intergroup differences in Epstein-Barr or human herpes virus antibody titres between the 2 groups.[262]

8.3.2 Enteroviruses

There have been reports that very strenuous exercise damages the intestines sufficiently to permit the penetration of endotoxins into the blood stream.[206,263] An enteroviral infection is thus a further theoretical possibility.

However, a blinded study found no enteroviral RNA in the sera of either patients with CFS or controls,[237] and a second comparison of 88 individuals with CFS with 77 healthy neighbourhood controls showed no differences in the prevalence of IgG and IgA antibodies to Yersinia enterocolitica outer membrane proteins.[247]

8.3.3 Poliomyelitis

Late fatigue is a common complaint of those surviving acute anterior poliomyelitis.[264] This could reflect, in part, the effects of residual muscular paralysis, although problems of attention, cognition and maintaining wakefulness mirror the neuropsychologic manifestations of CFS, suggesting some possibility of a common physiopathology.[248]

8.3.4 Rubella

Vaccination with live attenuated rubella virus can cause symptoms of fatigue. Complaints are associated with a low titre of antibodies 10 weeks after vaccination, and seem to be most common in individuals with high externalising scores on a personality questionnaire.[249]

8.3.5 Borna Disease

Borna disease is caused by a neurotropic virus. Nakaya et al.[238,239] described 2 family clusters of CFS where all affected members of the 2 families showed antibodies to this virus. The same authors reported a substantial prevalence of Borna disease in individuals with CFS (for example, 34% of Japanese patients with CFS).[238] However, Kubo et al.[243] observed no evidence of Borna disease virus in patients with psychiatric disorders, and Evengard et al.[265] found no specific immunoreactivity to Borna Disease virus in 169 individuals with CDC-defined CFS or in 62 controls.

8.3.6 Rickettsial Infections

A group of 71 patients who had been infected with Q fever 5 years earlier were compared with 142 age- and gender-matched controls; CDC criteria for CFS were met by 42% of those infected, compared with 26% of controls.[250] Similar findings have been reported in abattoir workers occupationally exposed to Q fever.[250]

8.3.7 Lyme Borreolis

Chronic Lyme Disease is another tick-borne infection characterised by a decrease in positive affect.[266] A prospective double-blind study of 1156 healthy young males searched for Borrelia antibodies. Seropositive individuals who had never developed clinical manifestations of Lyme borreolis nevertheless had a significantly higher prevalence of chronic fatigue and malaise than those who were seronegative.[251] But despite some overlap of symptomatology, patients with post-Lyme disease fatigue showed greater cognitive deficits than those with CFS.[267] Moreover, when analysis was restricted to 39 individuals with CDC-defined CFS, no laboratory evidence of *Borrelia burgdorferi* infection was found.[268]

8.3.8 Brucella

Mice injected with killed *Brucella abortus* showed evidence of fatigue relative to animals injected with a saline control; they began wheel run-

ning normally after the lights were extinguished, but unlike the control animals stopped from apparent fatigue after 1 to 2 hours.[252] However, a clear relationship to CFS has yet to be demonstrated.

8.3.9 Mycoplasmal Infections

Mycoplasma fermentans and other mycoplasmal species are colonisers of human mucosal surfaces. As many as 60% of patients with CFS have evidence of one or more types of mycoplasmal infection.[253] Analyses of peripheral blood mononuclear cells disclosed a higher prevalence of both mycoplasmal genomes and *Mycoplasma fermentans* in 100 cases of CFS (52 and 34%, respectively) than in 56 controls (14 and 8%, respectively), with corresponding differences in genome copy numbers and antibody titres.[254]

Although many potential micro-organisms have been investigated, there is as yet no conclusive evidence that any type of infection can cause CFS. On the other hand, it seems quite possible that acute infections can precipitate, exacerbate or maintain CFS,[10,269-271] and a chain reaction of overtraining, immunosuppression, enhanced susceptibility to infection and precipitation of CFS remains quite plausible in the high performance athlete.

9. Course of Disease and Response to Treatment

9.1 Course of Disease

The course of the disease is long, and spontaneous recovery can be a very incomplete process, particularly if analysis is restricted to cases where standardised criteria of diagnosis have been applied.[272] Studies of 'chronic fatigue' found 54 to 94% recovery in children, and (in cases of less than 6 months duration) 40% recovery in adults.[273] On the other hand, a review of 26 follow-up studies found 5 where CFS had been operationally defined; in these studies, less than 10% of patients returned to premorbid levels of functioning.[273]

A 4-year study of patients with severe manifestations of CFS found that 13 patients remained severely ill, 9 showed improvement but still maintained the CDC definition of CFS, and only one recovered.[274] Likewise, Bombardier and Buchwald[272] observed spontaneous recovery in only 2% of individuals over 18 months of observation. A study[275] of 25 cases in children who had been referred to a tertiary psychiatric clinic found a mean illness duration of 38 months. A follow-up questionnaire mailed to 341 adults who had been ill for an average of 9 years obtained 177 responses; only 21 individuals in this sample (12%) reported recovery, this being associated with higher levels of physical and social functioning, and lower levels of anxiety and obsessive compulsiveness.[276] Likewise, a follow-up averaging 3.2 years found improvement in only 6 of 28 patients.[277]

9.2 Treatment Options

There seems to be no universally effective therapy for CFS,[278] and as with overtraining, the response to treatment is often disappointing.

A survey of Irish general practitioners found 11 disparate approaches to treatment.[34] Often, patients and their physicians spent an inordinate amount of effort in searching for a 'cause', when energy might have been better directed to health promotion, particularly a programme of graded physical activity.[279-281] The usual approach is a combination of psychosocial therapy and encouragement.[282] Neither diet nor the administration of Ig appears to offer any consistent advantage over placebo treatments.[4] A reduction in psychological symptoms is usually associated with a decrease in fatigue, improved functioning and a return to work.[283]

9.3 Conditioning Exercise

Given that many of the manifestations of CFS are associated with a cessation of training and resultant deconditioning, it seems logical to encourage implementation of a carefully graded programme of conditioning as a central component of treatment once any precipitant such as infection or injury has been resolved.

A moderate and progressive increase over current levels of exercise may help give the patient a sense of control over the condition. On the other hand, a sudden return to an excessive level of phys-

ical activity can exacerbate symptoms. Management is thus based on the principle of avoiding setbacks in recovery by appropriate control of the level of exertion.[237,284,285] A careful recording of the frequency and intensity of physical activity and its correlation with self-reports of symptoms is sometimes helpful in setting an appropriate exercise prescription.[286] On the other hand, there are dangers in encouraging excessive self-monitoring, and in some instances it may be necessary to review inappropriate interpretations of normal responses to physical activity. Repetition of the activity is avoided if the resting heart rate increases by more than 20 beats/min.[287] In cases where there is a suspicion of infectious mononucleosis and clinical or ultrasonic evidence of splenic enlargement, it is prudent to avoid contact sports;[287,288] the incidence of splenic rupture in athletes following infectious mononucleosis has been set as high as 1 to 2 per 1000 individuals.[288]

A 6-month randomised blinded prospective trial[289] in 96 individuals with CFS, found that a graded exercise programme significantly improved both health perceptions and the sense of fatigue, whereas fluoxetine improved depression only. A second randomised crossover trial[290] compared graded aerobic exercise with flexibility and relaxation treatment. Ratings of perceived effort during submaximal exercise decreased in response to such conditioning.[290] Analysis by intention to treat found 17/33 versus 9/33 cases of CFS reporting improvement; fatigue, functional capacity and fitness were all significantly enhanced by the aerobic programme. Gains in aerobic power averaged a substantial 13%, although it is a little surprising that the changes in aerobic power and muscle strength were no greater in those who rated themselves as improved than in those who did not.[291] Furthermore, these 2 trials were necessarily based on that minority of patients (perhaps less than 10% of CFS cases) who were well enough to attend outpatient exercise sessions on a regular basis.[292,293]

10. Future Directions and Conclusions

Despite some progress over the past 5 years, many major issues remain to be resolved with regard to CFS. Is it one disease, or many? In the case of the high-performance athlete, is there a clear linkage to overtraining, resulting immunosuppression and development or reactivation of infection? Is there an objective decrement in physical performance, or do apparent changes reflect mainly effort avoidance by the patient, with resultant deconditioning? If micro-organisms play an important role in disease causation, is just one agent responsible, or can a variety of viruses and bacteria induce the syndrome? Most recent articles recommend a progressive exercise regimen as a part of treatment, but there is still a need to define the optimal pattern of reconditioning, and to decide how important a role is to be played by psychological counselling.

There seem no easy approaches to answering these questions. To date, much confusion has arisen from inadequate characterisation of patients and a failure to use controlled studies when examining disease aetiology and the response to treatment. Progress should be faster with acceptance of uniform descriptions of the syndrome and the trend to randomised, blinded studies of both the disease and therapeutic interventions.

For the present, we must conclude that CFS is a syndrome rather than a clear-cut disease, defined by a symptom-complex rather than clear physiological and biochemical manifestations. It affects both athletes and sedentary individuals. There have been reports of associations with excessive physical activity, nutritional deficiencies, immune disturbances, autonomic and hormonal dysfunction and viral infection. Nevertheless, none of these associations are consistent; likely, they represent precipitants or consequences rather than underlying causes of the syndrome. In the absence of a clear pathology, treatment remains unsatisfactory. In athletes where the condition has become established, the best advice seems to be to break the vicious cycle of effort avoidance, a resulting decline in physical condition and a deterioration of morale through a combination of encouragement and a carefully monitored progressive return to training.

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