
Chronic fatigue syndrome





To the Minister of Health, Welfare and Sport
PO Box 20350
2500 EJ The Hague

Subject : Submission of advisory report *Chronic Fatigue Syndrome*
Your ref. : POG/ZP 2.294.354
Our reference : I-707/YvD/sl/708-T
Appendices : 1
Date : 25 January 2005

Minister,

On 7 June 2002 your predecessor requested an advisory report about Chronic Fatigue Syndrome (CFS) from the Health Council of the Netherlands. In response to this request please find enclosed the advisory report *Chronic Fatigue Syndrome*, which a Health Council Committee drafted at my request and which was assessed by the Council's Standing Committee on Medicine. I wholeheartedly endorse the conclusions and recommendations of the Committee. I request you pay special attention to a number of issues.

There is meagre knowledge about fatigue and, in particular, chronic fatigue syndrome. Nonetheless, enough knowledge has gradually become available for the professional organisations to be requested to draw up guidelines for the treatment and supervision of patients with CFS, as recommended by the Committee. It would be of the utmost value if the results of the study you financed and that NIVEL conducted on assignment of the Health Council, could be included in this.

The request for an advisory report originated from the intention of your predecessor to take up scientific research of CFS through ZonMW. The advisory report raises the issue of numerous gaps in knowledge about CFS that call for further research. I endorse the view of the Committee that chronic fatigue syndrome must be considered an unexplained physical illness (a category to which, for example, fibromyalgia and irritable bowel syndrome also belong). With the benefit of the latest insights from the neurosciences, the Committee sketches a model that gives a multidimensional, process-oriented view of the causes and development of unexplained physical illnesses, including CFS, where proper attention is given to biological and psychosocial factors.

Gezondheidsraad

Health Council of the Netherlands



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I consider it important to emphasise that a search for one specific cause of CFS has little chance of success and actually broadening the insight into the causes and the treatment of CFS requires a multidisciplinary approach in which the various factors are coherently studied.

I have also brought the advisory report to the attention of your colleague from Social Affairs and Employment.

Yours faithfully,

(signed)

Professor JA Knottnerus

Chronic fatigue syndrome

to:

the Minister of Health, Welfare and Sport

No. 2005/02E, The Hague, 25 January 2005

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues...” (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.



The Health Council of the Netherlands is a member of INAHTA, the international network of health technology assessment (HTA) agencies that promotes and facilitates information exchange and collaboration among HTA agencies.

This report can be downloaded from www.healthcouncil.nl.

Preferred citation:

Health Council of the Netherlands. Chronic fatigue syndrome. The Hague: Health Council of the Netherlands, 2005; publication no. 2005/02E.

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ISBN: 90-5549-558-1

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Executive summary

Virtually everyone feels tired, or even exhausted, every now and again. We usually know why this has come about and the feeling wears off, either spontaneously or after a little extra rest. This is not the case with chronic fatigue syndrome (CFS). CFS patients feel perpetually tired and exhausted and also have a host of other physical complaints. CFS is also known as 'ME' (myalgic encephalomyelitis), a term that the Committee does not use since it erroneously implies the presence of an inflammation of the brain and spinal cord.

CFS is a controversial disorder. There are people both within and outside the world of medicine who believe that it does exist, and others who believe that it does not. This situation has given rise to major differences of opinion concerning the ability of CFS patients to work, and thus to their entitlement to social security benefit.

CFS is a genuine, severely incapacitating disorder. It is an established fact that CFS imposes limitations on an individual's personal, occupational and social functioning. The quality of life of CFS patients is lower than that of healthy people. The symptoms fluctuate, and this is unsettling for patients. They are forced to modify their activities, they no longer have the energy for social activities, working is often out of the question, contacts with colleagues gradually fall away, and their financial situation worsens. Not infrequently, they end up in social isolation.

Patients are reliant on help from others for their daily functioning. Onlookers do not always take their disorder seriously and dismissively suggest that 'it's probably psychological'. Patients expect their doctor to bring about an improvement in their condition,

but they are often told that the cause of these complaints is unknown and that there is no treatment. They hear stories (via the internet, a patients' organisation or those around them) about people who have had CFS for many years. They can easily get into a situation devoid of future prospects, which persists for many years. Spontaneous recovery is possible, but it is the exception rather than the rule. Such research as there is suggests that ten percent or less of adults with CFS recover spontaneously in the long term. For young patients, the prognosis is substantially better: the majority recover after a few months or a few years.

The internationally recognised case definition (CDC '94 criteria) is the standard.

Knowledge concerning the development and causes of CFS is inadequate, the symptoms are variable and not very specific, and there also are no straightforward diagnostic tests. One solution in instances of this type is a case definition (i.e. a consensus-based description of the disorder). The internationally recognised case definition of CFS is the one formulated by the US Centres for Disease Control (CDC) in 1994 (see panel). In order to

US Centres for Disease Control Case Definition of Chronic Fatigue Syndrome, 1994

Diagnostic criteria: At least 6 months of persistent or recurring fatigue for which no physical explanation has been found and which

- is of new onset, that is to say it has not been lifelong
- is not the result of ongoing exertion
- is not substantially alleviated by rest
- severely limits functioning

in combination with four or more of the following symptoms, persistent or regularly recurring over a period of six months and which must not have predated the fatigue:

- self-reported impairment in memory or concentration
- sore throat
- tender cervical lymph nodes
- muscle pain
- multijoint pains
- headache
- unrefreshing sleep
- post-exertional malaise lasting 24 hours or longer

Exclusionary criteria

- any medical condition that may explain the presence of chronic fatigue
- a psychotic, mayor or bipolar depressive disorder (but not an uncomplicated depression)
- dementia
- anorexia or bulimia nervosa
- alcohol abuse or the use of drugs
- severe obesity

broaden our understanding of the nature and course of the disorder, we recommend that the CDC-94 definition be applied by researchers and practitioners alike – which is not to say, however, that the research and treatment of chronic fatigue should be confined to those patients who satisfy the CDC-94 criteria.

Any case definition is a construct for the benefit of practitioners, with arbitrary elements and limitations. For example, the existence of criteria does not necessarily connote a disease (in the sense of a specific, well-defined pathological process) that corresponds to these criteria. That remains to be established. Limitations of the CDC definition lie in the fact that the symptom criteria have not been validated and that the definition was primarily formulated for scientific research purposes.

There are probably between 30,000 and 40,000 CFS patients in the Netherlands.

The Committee emphasises that this is no more than a rough estimate. Reliable epidemiological data concerning CFS are scarce. Variations in the applied case definitions and the fact that not all patients consult a general practitioner are to blame for this. The majority of the patients are adults, but the disorder also occurs in the young. Around three quarters of sufferers are women.

No prevalence figures are available for Belgium, France and Germany. Dutch data concerning CFS in people of different ethnic origin are likewise unavailable, nor is there any research into the question of whether CFS is more prevalent in certain occupations than in others.

The doctor-patient relationship influences the course of fatigue complaints.

The outcome of such complaints as chronic fatigue is determined not only by doctors' instrumental actions, but also by their affective actions. It is important that doctors should take both the complaints and the patients seriously, invest in establishing a good relationship with them, allow them to express their emotions and explain the different aspects of fatigue.

Rigid preconceptions concerning physical and psychological causes put pressure on the doctor-patient relationship and obstruct research progress. Physical and psychological causes of CFS are frequently considered as polar opposites. A question that patient organisations are again and again confronted with is whether CFS is a neurological or a psychiatric disorder. This is, in fact, a spurious question. The neuroscientific research conducted in recent decades has revealed that psychology (e.g. behaviour) and biology (e.g. biochemical processes) are, as it were, two sides of the same coin. It is not a question of either one or the other, but of both together. Acceptance of this idea fosters the necessary common perspective on the part of the doctor and the patient, and offers researchers fresh insights into the causes of CFS.

Drawing a distinction between aetiology and pathophysiology lends clarity to discussions over the causes of CFS. Whereas aetiology is concerned with the cause of a disorder (i.e. what circumstances make a person develop CFS?), pathophysiology is concerned with the manner in which it arises (i.e. what biological disturbances are involved?). This distinction is crucial, however, when it comes to sorting out the large body of data, which vary in their level of abstraction and are derived from different fields of research, and translating findings into new hypotheses for research. It also provides a good starting point for discussions with patients.

The aetiology of CFS is influenced by a range of factors. Aetiological factors are commonly broken down into the following categories:

- *Predisposing factors.* Factors that make one individual more likely to develop CFS than another: familial (possibly genetic) factors, sex, learning history (experiences in early youth), personality, lifestyle and physical activity.
- *Precipitating factors.* Factors that can provoke CFS in susceptible individuals: acute stress, both physical stress (a serious injury, chronic sleep disturbances, an invasive surgical procedure or an infection) and situations of acute psychological stress.
- *Perpetuating factors.* Factors that impede recovery: physical inactivity, periodic over-activity, incorrect or unhelpful notions about the disorder, increased attention to physical sensations, inappropriate behaviour on the part of care providers, and social factors. Despite frequent claims to the contrary, chronic infections are not a perpetuating factor.

Models derived from the modern neurosciences form a good basis for pathophysiological research into CFS. CFS is one of the many syndromes with physically unexplained symptoms (other examples being fibromyalgia and irritable bowel syndrome). Pathophysiological research has hitherto focused mainly on those aspects that distinguish a given syndrome from other syndromes, though this approach has proved rather unproductive. The syndromes frequently occur in combination and display striking similarities. The pattern of symptoms associated with these conditions points to a disruption of control systems or of communication between control systems. Marked deviations in individual parameters are rare. The disruption appears to have its origins in the same basic pattern: a long-term and serious disturbance of the balance between emotional endurance and stress. Situations of chronic stress cause an imbalance of homeostatic mechanisms (e.g. energy balance and recovery processes) and alter sensitivity to pain and perception. Well-substantiated explanatory models derived from the modern neurosciences support this line of argument. These models afford an opportunity to bridge the gulf between somatic and psychological factors and form a sound basis for the development of new research hypotheses.

‘To stand still is to move back’ is the starting point in the management of fatigue complaints. Fatigue is, generally speaking, a signal to take things easier, but absolute rest is not beneficial and ultimately perpetuates the complaints. Patients with fatigue complaints should be advised to do whatever they still can, if necessary after having adjusted their work and/or working hours in consultation with either the occupational physician or – if the patient is unemployed – with other members of the household. Although a patient may well be (temporarily) unfit to perform his job, this need not mean that he is totally unfit for work. Fatigue frequently has an ‘everyday’ cause such as overwork or stress. Recovery is dependent on the patient facing up to these causes and actively addressing them. Rest by itself can reinforce avoidance tendencies, prolong sick leave and set in motion a process of social marginalisation.

Openness is essential when assessing fitness for work. This is important in order to avoid (where possible) the many misconceptions and differences of opinion that surround CFS patients’ fitness for work. One such misconception is the belief that the diagnosis and the cause of a disorder are what determine a person’s entitlement to absence from work or to receive social security benefit. It is the responsibility of occupational physicians and insurance physicians to explain that manifestations and consequences of illness are what matters, and that the assessment of fitness for work hinges on three issues:

- *General functioning:* Someone who, as a result of disease or infirmity, generally speaking cannot function is also unable to work. If he is, in fact, able to function to some extent, then certain forms of work will also soon be possible.
- *Consistency:* of reduced fitness for work can only be said to apply where there is a logical and consistent relationship between illness, limitations and a decline in work participation. If that is not the case, then there is no incapacity due to illness.
- *Problem analysis:* People’s stress load is only partly determined by working conditions. In addition to the medical aspects, an insight into the psychosocial context plays an essential role when forming an opinion on an individual’s fitness for work.

Proper patient care requires guidelines for the diagnosis and support of patients with fatigue complaints. There is great variation in the diagnosis and support of patients with fatigue complaints (and especially those with CFS). This applies both to the procedures followed by general practitioners as well as to those adopted by occupational and insurance physicians. Patients have a right to uniform treatment and procedures. The Committee explains the broad principles to be applied with fatigue complaints (and especially CFS). Translating these into policy guidelines is a matter for the Netherlands Society of General Medical Practitioners (NHG), the Institute for Healthcare (CBO), the Association for Medical Services in Industry (NVvAB), and the

Association for Insurance Medicine (NVVG). First of all, however, it is imperative that they should come together to agree on a common set of basic principles and on collaboration in this area.

Special attention is required for CFS in young people. Youngsters with CFS are frequently no longer able to follow a standard school curriculum, do homework, cycle or walk normal distances, or take part in sports and other social activities. CFS threatens normal, age-appropriate development, such as the pursuit of autonomy and identity, and separation from one's parents.

Doctors are advised against making the diagnosis of CFS before a child reaches the age of 10, since the presentation of symptoms at that age is, to a great extent, dependent on the way in which they are interpreted by the parents. Non-functional attributions by the parents can stand in the way of the youngster's recovery. It is therefore advisable to separately speak with the patient and the parents. This also fosters a feeling of autonomy in the youngster.

Cognitive behavioural therapy (CBT) is an effective treatment. There is no shortage of treatments for CFS – especially on the internet – but few have been tested for efficacy. The systematic reviews that have been conducted of interventions for CFS reveal CBT to be an effective treatment.

CBT has been successfully applied in several places to patients with CFS. The therapeutic effect has proved to be long-lasting and no deterioration has been shown to occur as a result of this therapy. However, CBT is not a panacea. The therapy is intensive, makes great demands on the patient and has a success rate of around 70%. Success means that the patient is restored to a more or less normal level of functioning. However, many successfully treated patients will no longer return to their former level of functioning, but have learned to adapt to the constraints imposed by their illness. Some people experience this as a loss that they must accept. Self-efficacy is an essential element in CBT. It is extremely important to motivate patients to undergo the therapy. CBT is inextricably bound up with a gradual stepping-up of physical activity ('graded exercise training', GET). Whether GET is effective without any form of CBT is being investigated at this moment in the UK.

The patient population is diverse and not everyone benefits from CBT according to the current protocol. The development of additional, less intensive variants of CBT will make it possible to bring supply more into line with demand.

Treatment capacity needs to be expanded. CBT for CFS patients is only available on a formal basis in Nijmegen, and there are around 300 patients on the waiting list. In order to provide proper patient care, treatment capacity needs to be expanded, for exam-

ple by establishing centres along the lines of the Nijmegen model or centres for the research and treatment of stress-related conditions. One problem hampering efforts to scale up this capacity is the fact that very few psychologists possess the requisite expertise. More attention needs to be given in the training of psychologists to the use of behavioural therapy to treat physical complaints (not only for the treatment of patients with CFS but for all patients with physically unexplained complaints).

Sound scientific research into CFS requires a multidisciplinary approach. Large gaps exist in our knowledge of CFS. Countless unresolved questions require new scientific research. The search for a single, specific cause of CFS has proved fruitless and will probably not lead to an explanation of the range of symptoms and associated phenomena. If we are to succeed in actually expanding our understanding of the causes and the treatment of CFS, then a multidisciplinary approach will be required in which the interrelationships between the various factors are studied.

Introduction

In July 2002 the Minister of Health, Welfare and Sport requested advice from the Health Council on the current level of knowledge regarding chronic fatigue syndrome (CFS) and its significance for the treatment and care of patients with this condition (Annex A). On 16 December 2002 the President of the Health Council set up a Committee to answer the underlying questions (Annex B).

1.1 About CFS

Virtually everyone feels tired, or even exhausted, every now and again. We usually know why this has come about and the feeling wears off, either spontaneously or after a little extra rest. CFS is characterised by prolonged fatigue and exhaustion in combination with other symptoms, including muscle pain, headache, unrefreshing sleep, sore throat and a feeling of malaise after exertion. The precise number of CFS patients in the Netherlands is not known, but probably lies between 30,000 and 40,000. The majority of the patients are adults, but the condition also occurs in young people. Around three quarters of CFS patients are women.

CFS imposes considerable limitations on an individual's functioning. The nature and origin of the condition are surrounded by ambiguity and uncertainty, which is frustrating for the patients and their carers, and also for physicians and other care providers. CFS has been the subject of extensive study over the past 15 years¹²⁸. Within the scientific community, this has led to widespread support for the view that a strict, biomedical perspective will not suffice and that the only fruitful approach is a 'biopsychosocial' one

involving integration with a social and psychological frame of reference^{6,233,334}. There is a persistent lack of consensus, however, when it comes to concretisation.

CFS is better known to the general public as ‘ME’, an abbreviation that stands for ‘myalgic encephalomyelitis’. This diagnosis was introduced in 1955 for a clinical picture consisting of muscle pain and fatigue, which had been identified among the staff (but not among the patients) of the Royal Free Hospital in London. Myalgic encephalomyelitis is a misleading name, since it implies muscle pains caused by an inflammation of the brain and spinal cord, whereas there is no evidence to support this. In the international scientific literature, the term ME has meanwhile been almost completely superseded by CFS (chronic fatigue syndrome)^{3,233}. This term dates back to 1988, when Holmes introduced a case definition for a collection of signs and symptoms that had been known by various names for more than two centuries and had been attributed to a variety of causes during this period¹³⁹.

Outside scientific circles, the term ‘ME’ is still in vogue, with its implicit connotations of ‘mysteriousness’ and incurability. The Dutch patient organisations* have retained ME in their name since they feel that a name change would be detrimental to their public profile. They generally use ‘ME’ or ‘ME/CFS’ in their publications. In the US, two terms are also in use that are less common here: CFIDS (chronic fatigue and immune dysfunction syndrome) and CNDS (chronic neuroendocrine-immune dysfunction). The name is a constant topic of discussion, with the key criticism being that the term CFS is euphemistic and takes insufficient account of the patients’ other symptoms^{147,148,327}.

1.2 About the advisory report

Behind the squabbling over the name lurk arguments of a more fundamental nature. Although the Committee will not duck these issues, it does not presume to be able to resolve all of them definitively. It reviews the current level of knowledge, draws attention to gaps in our knowledge and makes suggestions regarding promising avenues of research.

CFS is an emotionally charged topic. In Chapter 2 the Committee outlines the background to this controversy. The definition and classification of CFS are the focal point of Chapter 3. In Chapter 4 the spotlight falls on the epidemiological data. In the fifth chapter the Committee formulates hypotheses regarding aetiology and pathogenesis that are based on the available scientific data and that may point the way for research into CFS.

* *ME/CVS-Stichting* [ME/CFS Foundation]; *Steungroep ME en Arbeidsongeschiktheid* [ME and Disability Support Group]; *ME-Fonds* [ME Fund] (closed down on 1 January 2004); MEDIVERA, CFS/ME patient interest group (since 6 May 2003, formerly: *ME/CVS-huis*)

The next two chapters are devoted to the diagnosis, support and treatment of CFS patients. Chapter 6 is concerned with general developments and Chapter 7 looks at the young CFS patient. In the eighth and final chapter, the Committee looks in some detail at scientific research into CFS.

The Committee conforms to the practice of using the male pronoun, despite the fact that the vast majority of CFS patients are women. Nevertheless, 'he', 'him' and 'his' can equally be read as 'she' and 'her'.

The context

CFS is generally acknowledged to be a controversial condition. The suffering of the patients is not at issue here. The points of contention are how far and in what way physiological, social and psychological factors contribute to the condition and whether it is a specific, homogeneous clinical entity with its own pathogenesis or a condition that is triggered by a variety of circumstances. CFS ‘believers’ and CFS ‘non-believers’ are to be found both within and outside the world of medicine^{22,307,338}. This situation has repercussions for the communication between physicians and patients and has led to major differences of opinion regarding the ability of CFS patients to work and their entitlement to social security benefit.

2.1 The daily life of the CFS patient

CFS has a major impact on the day-to-day life of the patient. Patients frequently feel tired from the moment they get up, despite having had a long night’s sleep. Pain in muscles and joints, and influenza-like symptoms, contribute to the feeling of malaise and exhaustion. In addition, they are sometimes also troubled by forgetfulness, concentration problems, dizziness and sleeping problems. The fatigue and accompanying symptoms impose severe limitations on personal, occupational and social functioning^{6,34,118,136,262,316}.

The symptoms fluctuate. The patients have good and bad days, and it is this unpredictability that gives rise to their uncertainty. Although not everyone is affected to the same extent, all patients have to modify their pattern of activities. The way in which

they do this varies. Some people continue working for as long as possible at the expense of domestic and social activities, while others stop working in order to devote their limited energies to household tasks and self-care. There are also patients who hand over all their tasks to others and spend a large part of the day in bed in the hope that rest will help^{26,106,129,260,299,329}.

Not infrequently, patients withdraw into social isolation^{14,95,236,260,329}. Since they lack the energy to take part in organised activities, the associated social contacts rapidly decline. Many people find it difficult to make or receive visits. Some even find a telephone conversation too demanding. Partial or total incapacity for work is common, with the result that contacts with colleagues gradually fall away and their financial situation worsens^{34,118,192,298,329}.

Patients are primarily reliant on other members of the household for help with daily functioning. Sometimes there are friends who step in or homecare is provided (though this happens less often than one would like). Single people usually have more difficulties than people with a partner, although this relationship can come under severe pressure owing to their greater dependence on the other person. The fact that no physical explanation has been found for the symptoms and that patients display no visible signs mean that family and friends do not always take their condition seriously and dismissively suggest that 'it's probably psychological' – a reaction that patients vehemently resist^{12,14,16,34,95,118}.

The quality of life of CFS patients is significantly lower than that of healthy individuals^{129,304}. Patients find themselves in a situation with few future prospects. They go to their physician in the expectation that he may bring about an improvement in their condition, but they are frequently told that he can find no cause for their symptoms and that there is no treatment. They hear stories (via the internet, patients' organisations or those around them) about people who have had CFS for many years, whereupon they may easily give up all hope of improvement and either adapt to their situation or else slide into apathy, despondency and impotence.

2.2 Recognition

It is enormously important for anyone who has a serious problem that it should be recognised by others. Patients consequently attach great importance to the receipt of a diagnosis, which they regard as a sign that they are being taken seriously. It also provides relief and an opportunity to accordingly re-organise their lives. A diagnosis provides a basis for discussions about the demands that can be made on the patient, a bona fide reason for their role as an 'invalid', and it also paves the way for practical assistance and services. Furthermore, a diagnosis helps patients make meaning of the bewildering changes that they are experiencing in their bodies and their functioning^{242,269,317}.

Numerous vivid accounts can be found on the internet and in the patient literature about the difficulties that patients encounter in obtaining a diagnosis (see also the discussion paper on the problems of CFS [*Knelpuntennota*] in Annex A). Physicians reportedly fail to take their symptoms seriously and fob them off, stating that there is nothing wrong with them^{90,174,329}. Lack of recognition is an important source of dissatisfaction and can lead to tensions in the consulting room (2.4, 2.5) and to conflicts with employers, occupational physicians and benefit agencies. These conflicts can, in some cases, result in many years of wrangling and appeals procedures concerning the degree of fitness for work.

2.3 The expert patient

Cultural, political and social influences partly determine the way in which people perceive their illnesses, symptoms and infirmities, and possibly also the way in which they present their symptoms^{238,310}. A great fascination with sickness and health is a feature of the times in which we are living^{265,344}. Newspapers, magazines, radio and TV provide the public with an important – though by no means always accurate – source of medical information. More recently, people have also used the internet, in particular, in order to gather information about their symptoms and infirmities. The internet offers an abundance of information on CFS (ME) and possible interventions, especially on the websites of patient organisations and pressure groups. National borders are of little or no significance on the internet. Many sites give the same prominence to unproven, ‘alternative’ or commercially biased therapies as they do to interventions whose efficacy is firmly established^{19,113,162}. In addition, CFS is frequently also depicted as a strictly physical disorder. On certain sites – some of them in Dutch* – treatments of proven efficacy (e.g. behavioural therapy, Chapter 6) are disputed in highly emotional terms.

The patient has become involved in the discussion over what constitutes a disease and what a constitutes good physician, and how their symptoms should be treated. Some patients with CFS regard themselves as the experts who should instruct and inform the physician about developments in this field^{13,64} – a situation that some physicians are better able to cope with than others.

2.4 In the consulting room

Fatigue is an intangible symptom. It is an extremely common symptom and a frequent reason for visiting a general practitioner. There is virtually no disorder or disease in

* Cognitive behavioural therapy in people with ME/CVS: Standpoint of the ME and Disability Support Group. <http://www.steungroep.nl/cgt/cgtstandpunt.htm> (in Dutch; consulted on 20 December 2004).

which fatigue does not occur as a secondary symptom. Of all the symptoms presented to GPs, 25.4% involve fatigue (in some cases in conjunction with other symptoms). Fatigue thus ranks 14th in the list of symptoms and disorders presented to general practitioners in the Netherlands²⁹³. It is therefore not particularly surprising that a GP would not immediately think of CFS on being presented with fatigue as a primary symptom. Fatigue is not specific, it can only be measured by questioning patients, and it is of limited duration in the majority of patients (6.2).

Patients and patient organisations often complain that physicians (and especially GPs) do not take them seriously. Physicians are accused of not giving them enough time, not being open to their story, not recognising their problems, making them feel guilty, and adopting a paternalistic attitude^{75,95,217,238,260}. Even some Dutch GPs are disinclined to make the diagnosis of CFS^{27,217,*}. The latest survey indicated that half of the participating group of Dutch GPs do not make the diagnosis of CFS when this would, in fact, be appropriate and that they also only confirm this diagnosis in a quarter of the patients who present with a self-diagnosis of CFS (two thirds are self-diagnosed)³². Patient organisations (see discussion paper [*Knelpuntennota*], Annex A) argue that physicians do not accept the diagnosis of CFS/ME because a laboratory test has yet to be developed that can detect the disease. In reality, the situation is rather more complex.

Failure to make the diagnosis of CFS, even though this would, in fact, be appropriate, is often due to unfamiliarity with the clinical picture. In some cases it is also due to a feeling of powerlessness on the part of the physician insofar as he feels that he has nothing to offer these patients from a therapeutic point of view^{217,220,303,c}. A further aspect is possibly the fear that the diagnosis of CFS may become a self-fulfilling prophecy and the patient will start to behave in accordance with the clinical picture. In addition, CFS patients have the reputation among physicians of being difficult to deal with and time-consuming. The diagnosis of CFS might reinforce this tendency^{95,236}. A further reason for not making the diagnosis of CFS is doubt as to its validity^{31,64,211,217,220,235,268}. The Committee points out that the diagnosis of CFS actually clarifies the situation and indicates how the patient might be managed. In point of fact, the Committee has evidence to suggest that Dutch physicians are slowly but surely becoming more amenable to the diagnosis of CFS.

CFS patients are often convinced that they have a purely somatic disorder. From the patient's perspective, his body is the site of the pain and the cause of his woes, and it is his body that has landed him at the physician's office³¹¹. Friction can easily arise if the patient's interpretation of his symptoms does not match that of his physician^{19,32,95}.

* Klein Rouweler E., Bleijenberg G, Severens H. Research into the prevalence of chronic fatigue syndrome as identified by GPs in the Netherlands and the attitude of GPs to chronic fatigue syndrome. Internal report (in Dutch), Nijmegen University Hospital, October 1999.

Patients who present with a self-diagnosis of ME or CFS often raise their physician's hackles. They are preoccupied with getting a biomedical diagnosis and find it difficult to accept being told that there is nothing physically wrong with them. Even physicians who do, in fact, make the diagnosis of CFS but at the same time point out the psychosocial aspects of the condition, or physicians who suggest putting the patient in contact with a psychologist, often meet with resistance^{12,19,90,220,235,242,269}.

In an effort to gain recognition for the existence of a somatic basis to their symptoms, many CFS patients turn to a specialist or an alternative healer (preferably someone who is known for his belief in the condition)^{19,34,64,211,298,329,335}.

2.5 Challenges

A shared, common perspective is a prerequisite for effective cooperation between physician and patient and is, in itself, of therapeutic value. Deficient communication skills on the part of physicians, and firmly held views about aetiology and treatment on the part of patients and their organisations, stand in the way of this common perspective^{11,15,21,127,220,242,266}.

If you need to prove that you are ill, then you cannot get better. Physicians ought to be more aware of the importance of respect for the patient's views and of recognising his suffering. That means focusing attention on the patient's story and listening actively^{116,127,143,309}.

The Committee consisted of two GPs, two internists, a psychologist, two psychiatrists, two experts in occupational health, the director of the Netherlands Institute for Research into Health Care (NIVEL) and a psychoneuroimmunologist. The Committee also had an independent chairman (Annex B). Nevertheless, the four patient organisations and a number of individuals have criticised the Health Council for allegedly skewing the membership of the Committee in favour of psychology. Patient organisations regard CFS as a purely physical disorder. Their point of view leaves little room for its psychosocial aspects. Their motivation is probably that this is more likely to give patients the status of 'genuine' invalids, meaning they are protected from the dreaded psychiatric stigma and run less risk of suffering from a 'non-disease' that does not require treatment and for which it is more difficult to demonstrate entitlement to receive social security benefit under the national disability insurance (WAO) scheme^{259,308,335}. A contributory factor to the fear of psychological and psychiatric explanations is the widely held belief that something 'physical' simply happens to you, whereas something 'psychological' is, to a certain extent, your own fault. In other words, you have no control over physical disorders (they are morally neutral), whereas you bear personal responsibility for psychological disorders^{73,242}. Such notions, prejudices and stigmas arise from the centuries-old portrayal of mankind in which body and mind are two quite

separate entities. This distinction cannot be maintained given the current level of knowledge.

The idea that, in addition to biomedical factors, psychological and social factors can also exert an influence over disease and perceptions of disease is not new. Now, however, we are also – slowly but surely – gaining an insight into possible mechanisms whereby these factors may influence one another (Chapter 5). These insights must be the guiding principle in shaping the essential common perspective on the part of the physician and the patient. It is up to physicians, patients and patient organisations to accept and adopt this way of thinking.

Definition and classification

Chronic disorders are often difficult to define. This is especially the case if knowledge concerning origin (aetiology) and disease mechanisms (pathophysiology) is inadequate, the symptoms are variable and non-specific, and no diagnostic tests are available. In such cases, medical science resorts to the formulation of ‘case definitions’ (consensus-based descriptions of disorders)^{10,145}. Examples are carpal tunnel syndrome, rheumatoid arthritis, the chronic variant of Lyme disease, dementia and various psychiatric disorders. CFS is another such poorly understood and difficult-to-define disorder.

3.1 Case definition of CFS

CFS is portrayed in the media as a ‘modern’ disease. However, the collection of signs and symptoms associated with this disorder have been known for several centuries under various names. In 1988 the US Centers for Disease Control (CDC) published a case definition for what they termed ‘chronic fatigue syndrome’¹³⁹. Various other definitions followed, including the widely used Australian (1990)¹⁷⁹ and British (1991)²⁴⁹ versions, and a revised CDC definition (1994)¹⁰⁹. This version (CDC-94) enjoys widespread support in scientific circles and can be regarded as the current standard^{3,224,233}. Finally, a proposal for a new definition was recently made by a group of scientists who are convinced that CFS stems from disruption caused by a viral infection⁵⁰. This definition only selects an extremely small group of patients with chronic fatigue symptoms. The Committee fears that this one-sided representation of the situation will not advance the research in this field (5.4.4).

A syndrome is a combination or succession of inter-related symptoms. In CFS, the primary symptom is severe fatigue that the patient has not previously experienced and that considerably increases in severity upon exertion. Secondary symptoms include headache, muscle and joint pains, cognitive problems (impaired memory and concentration) and sleeping problems. The symptoms must last six months or longer and severely limit daily functioning (see panel).

The definition and classification of diseases should ideally be based on knowledge of causal mechanisms. No specific disease mechanism has been determined for CFS; there are only hypotheses (Chapter 5). In this sense, CFS is not a disease but an illness^{191,*}: a description of a particular pattern of symptoms¹⁰. It should be noted that uncertainty over the disease process in no way detracts from the reality and the seriousness of the suffering and the limitations that are experienced by patients with CFS.

3.2 The definition in clinical practice

Diagnostic criteria are important for communication and decision-making, as well as being a necessary condition when comparing the outcomes of scientific research. The various definitions that are in circulation (3.1) select different patient populations^{41,149}. To increase understanding of the condition, it is advisable to apply the internationally recognised definition in research and in practice. That is not to say, however, that research and treatment of chronic fatigue should necessarily be confined to patients who satisfy the CDC-94 criteria.

The CDC-94 criteria have their limitations. They were drawn up for scientific research, not for clinical practice. This means that the definition is aimed at obtaining a homogeneous study group. Moreover, the underpinning of the criteria, and in particular those relating to the various secondary symptoms, is weak. These are consensus-based operational criteria that are based on the anecdotal experience of the authors and have not been empirically validated. Furthermore, there are arbitrary aspects to the process of determining the presence or absence of a particular symptom, since an outsider cannot measure the symptoms in question, but can only ascertain them through the patient's story. A further constraint that is sometimes mentioned is the fact that the criteria have been developed with an infectious cause in mind^{107,177,227,250,278}. Other people believe that insufficient account has been taken of the infectious nature of the syndrome^{50,177}.

* Dutch has no equivalent pair of terms¹⁹¹.

US Centres for Disease Control Case Definition of Chronic Fatigue Syndrome (CDC-94)¹⁰⁹

Diagnostic criteria: At least 6 months of persistent or recurring fatigue for which no physical explanation has been found and which

- is of new onset, that is to say it has not been lifelong
- is not the result of ongoing exertion
- is not substantially alleviated by rest
- severely limits functioning

in combination with four or more of the following symptoms, persistent or regularly recurring over a period of six months and which must not have predated the fatigue:

- self-reported impairment in memory or concentration
- sore throat
- tender cervical lymph nodes
- muscle pain
- multijoint pains
- headache
- unrefreshing sleep
- post-exertional malaise lasting 24 hours or longer

Exclusionary criteria

- any medical condition that may explain the presence of chronic fatigue
- a psychotic, major or bipolar depressive disorder (but not an uncomplicated depression)
- dementia
- anorexia or bulimia nervosa
- alcohol abuse or the use of drugs
- severe obesity

The CDC-94 case definition can be said to lift a particular patient group out of a far larger group of patients with chronic fatigue, without there being any hard evidence that a distinct clinical entity is being identified or that patients who do not exactly conform to the criteria have a completely different type of illness. If a patient with CFS-like symptoms does not entirely satisfy all of the criteria, then he is said to have ‘idiopathic chronic fatigue’ (ICF). The distinction between CFS and ICF has had no implications up to now as far as treatment is concerned (6.5).

3.3 **Overlap with other clinical pictures and comorbidity**

3.3.1 *Unexplained physical illnesses*

There is a substantial overlap with other unexplained physical illnesses, such as fibromyalgia (FM), irritable bowel syndrome (IBS), multiple chemical sensitivity (MCS) and particular war syndromes^{4,5,20,37,46,61,91,233,272,285,308,344}. The overlap with FM, in particu-

lar, is considerable. The symptoms of CFS and FM are comparable, but in CFS patients it is the fatigue that predominates, whereas with FM it is the pain.

3.3.2 *Depressive disorders*

There is a strong correlation between the number of non-specific physical symptoms that CFS patients report and the presence of psychological symptoms. In particular, the combination of depression and CFS is frequently mentioned^{89,146,173,232,253,254,286,288}, although the reported percentages vary markedly from around 35 to 65%. This is due to variations in the meaning of the terms ‘depression’ and ‘combination’. The senses in which ‘depression’ is used in the various studies range from depressive feelings up to and including severe depression. And whereas in one study ‘combination’ implies that the individual(s) concerned has (have), at some time, experienced depression, in another it implies the coexistence of CFS and depression. Depressive feelings occur in connection with numerous chronic physical disorders^{92,205,209}. CFS patients are evidently no exception. It is also clear that CFS can occur simultaneously with a depressive disorder. This is the case in 10 to 30% of CFS patients²¹⁶. This figure is higher than one would expect from the prevalence in the general population, where 15-25% of people experience depression at some point^{9,349}, but probably not much higher than is the case with other chronic physical disorders. CFS is distinguished from depressive disorder on the basis of the symptoms. If CFS and depression occur simultaneously, then comorbidity is assumed.

3.3.3 *Somatoform disorders*

The connection between CFS and somatoform disorders is confusing. According to the DSM-IV psychiatric classification system, somatoform disorders are characterised by physical symptoms that are not adequately explained by a known physical illness⁹. In this sense, CFS should be classified among the somatoform disorders. In the International Classification of Diseases (ICD-10), CFS is classified as neurasthenia³⁴⁹. DSM-IV and ICD-10 are merely descriptive classification systems. The mere fact that a condition such as CFS satisfies the criteria for a disorder that is described in DSM-IV or ICD-10 does not necessarily mean that it is therefore a well-defined psychiatric picture or that it is caused only by psychological factors (see also 3.4.3). Because of outmoded notions about ‘psychogenesis’ and the connotations of hypochondria and unconscious simulation that are associated with these psychiatric labels, the Committee does not find it particularly helpful to use this psychiatric terminology in relation to CFS^{46,247,305,349}.

3.3.4 *Overexertion and burnout*

Overexertion is characterised by exhaustion and tenseness. The symptoms worsen under the influence of (work)load and show little or no response to rest. Patients and care givers perceive overexertion to be the result of stress. The period between the start of the identifiable, stress-causing situation and the onset of functional problems is relatively short (up to around 12 weeks). A variety of stressors (e.g. overwork, life events and problems) can cause an individual to overexert himself, giving rise to an imbalance between stress load and emotional endurance. The pathophysiology is unknown. There follows a short period of ‘marking time’, in which the person concerned learns how to cope with the overwork in other ways. This usually leads within a short time (3 to 6 months) to the disappearance of the symptoms and functioning is restored²⁸³.

A hallmark of burnout is emotional exhaustion, which usually also manifests physically, grows worse under the influence of (even the slightest) exertion and shows little or no response to rest. There is no generally accepted definition of burnout, though various descriptions exist^{45,219,300}. Burnout is associated with a decline in commitment to work, reduced competence in the workplace, or both¹⁸⁷. The cause lies, by definition, in chronic work stress. The individual concerned will have a relatively long history of overwork (1 year or more). The symptoms are chronic. As far as pathophysiology is concerned, there are believed to be disturbances of neuropsychological, neuroendocrine and immunological processes (caused by prolonged stress), but this has not been conclusively proven^{240,301}. It is presumed that this disturbance can be cured over time through the correct combination of physical activity and rest.

The distinctions between overexertion, burnout and CFS seldom, if ever, lie in the symptoms or the social dysfunction. The respective clinical pictures are characterised, at most, by semantic differences of emphasis: fatigue in CFS and emotional exhaustion in burnout. What distinguishes CFS from burnout and overexertion is a marked tendency towards somatic attribution, i.e. CFS patients are inclined to attribute their symptoms to a physical illness. In burnout and overexertion, the symptoms are, in the first instance, interpreted psychologically (stress). In burnout patients, this may, in fact, even tip over into more somatically oriented attribution (disturbance of neuroendocrine and immunological processes). Recent research in the Netherlands confirms this view¹⁴⁴.

3.4 **Pitfalls of classification**

An unexplained syndrome is not a medical disorder with unequivocally definable natural boundaries. The case definition of an unexplained syndrome is a construct for the benefit of practitioners. In other words, the existence of criteria does not necessarily

connote a disease – in the sense of a specific, well-defined pathological process – that corresponds to these criteria. The case definition of CFS is thus inevitably arbitrary and, at the same time, it determines the extent and the nature of the patient population. Owing to the unexplained nature of the syndrome, it is not possible to test the validity of the criteria against a more general principal – a limitation that applies, in any case, to all unexplained physical syndromes^{80,177,227}. As a result, questions are continually arising to which there is no conclusive answer based on current knowledge, and from time to time it is proposed that the case definition be modified²²⁴.

3.4.1 *A distinct clinical entity?*

One of these questions is whether CFS should be regarded as a distinct clinical entity with an as yet unknown aetiology, or whether it ought to be interpreted as the extreme of a continuum of unexplained fatigue^{79,146}. The current level of knowledge does not provide a definite answer to this question. There is no sharp boundary between everyday fatigue and abnormal fatigue as manifested in CFS. Clinical practice does, however, identify clear-cut, qualitative distinctions between these two states and this also ties in with the experience of the patients themselves. The Committee considers it useful for practitioners to regard CFS as a discrete disorder.

3.4.2 *'Lumpers' versus 'splitters'*

There is a group of clinical researchers who view CFS as a particular segment in the spectrum of unexplained physical illnesses that also includes such conditions as FM, MCS, certain war syndromes and 'sick building syndrome'. They believe that it is worthwhile to take the similarities between these disorders as a starting point for further research^{4,22,46,91,203,243,265,266,338}. People who subscribe to this view are referred to as 'lumpers'.

There are also those who advocate the very opposite. These researchers – the so-called 'splitters' – would like to divide CFS patients into subgroups in order to reduce the heterogeneity, which they attribute to the CDC-94 criteria. Many proposals have been made as to how these patients could be split up, e.g. according to the duration of the illness, the nature or severity of the symptoms, the type of symptoms that are most prominent, functional capacity, personality, psychological comorbidity and the presence or absence of an antecedent infection^{106,152,153,188,189,251,278,319}. This approach has yet to produce any useful knowledge.

3.4.3 *Neurologic or psychiatric?*

The problem of diagnostic classification has already been touched upon in section 3.3.3. The place of CFS in the classification systems is confusing. In the international classification of psychiatric disorders, DSM-IV⁹, fatigue without any physical explanation fits into the category of undifferentiated somatoform disorders. In the international classification system for all diseases (ICD-10³⁴⁹), the disorder is mentioned under the neurologic diseases as post viral fatigue syndrome/benign myalgic encephalomyelitis (G93.3). In this same system, CFS can also be designated as a psychiatric disorder – neurasthenia (F48.0) – based on the symptomology. Over the years, many people have pointed out the resemblance between CFS and this particular clinical disorder, which was first described in 1869²⁴¹.

For reasons that were outlined earlier, CFS patients and their organisations insist on classifying their condition as a neurologic (i.e. somatic) disease. The Committee argues, however, that the place of CFS in a classification system says nothing about the nature of the illness and that the CFS case definition is no more than a description of a pattern of symptoms that cannot have any bearing on a discussion about whether it is ‘neurologic or psychiatric’. Furthermore, the Committee does not consider such a discussion to be helpful as far as the treatment of patients is concerned. The level of suffering and loss of function that are experienced are more important than the question of under which heading CFS belongs. Moreover, as has already been stated, the current level of knowledge argues against such a division, however socially ingrained this point of view might be.

Data

The basic questions to be answered when studying a particular disorder are: How common is it? Who does it affect? What course does it take? And, having explored these issues: How representative are the studies? What is the situation in our own country, the Netherlands? The data presented below relate to patients aged 18 years and over. The situation in young people is examined in Chapter 7.

4.1 International data

4.1.1 *How common is CFS?*

The prevalence of CFS is not easy to determine. Table 4.1 provides an overview of the outcomes of studies that have addressed this question. These are studies conducted since 1990 (either in the primary-care setting or in the population as a whole), involving more than 100 adult participants, and in which at least one of the known definitions of CFS has been applied. The findings (i.e. the measured prevalences) vary enormously. The studies in which various definitions have been juxtaposed clearly show that the prevalences depend to a great extent on which definition is applied. Also noticeable is the fact that the prevalences measured by means of self-reporting usually turn out higher than those based on diagnosis by a physician. If we only consider the studies in which the CDC-94 criteria have been applied and which are based on a physician's diagnosis, then only two studies remain, with a prevalence of 235 and 420 per 100,000 people, respectively^{150,229}.

Table 4.1 Prevalence of CFS per 100,000 people and the ratio between women and men.

Study	Criteria	Prevalence ^a	F:M
General population			
Reyes 2003 ²²⁹ US	people ≥ 18 years diagnosis by physician	CDC-94 ¹⁰⁹ 235	4.5:1
Lindale 2002 ¹⁷⁶ Iceland	people 19-75 years self-reporting	CDC-94 1,350 Oxford ²⁴⁹ 2,350 Australia ¹⁷⁹ 4,800 CDC-88 ¹³⁹ 0	3.3 :1 3.6:1 5.7:1
Jason 1999 ¹⁵⁰ US	people ≥ 18 years diagnosis by physician	CDC-94 420	1.8:1
Kawakami 1998 ¹⁵⁸ Japan	people ≥ 18 years self-reporting	CDC-94 1,460 Oxford 1,460 CDC-88 0	? ^b
Steele 1998 ²⁶⁷ US	people ≥ 18 years self-reporting	CDC-94 290	3.1:1
Lawrie 1997 ¹⁶⁹ UK	people ≥ 18 years self-reporting	Oxford 740	?
Lawrie 1995 ¹⁷⁰ UK	people ≥ 18 years self-reporting	Oxford 560	?
Jason 1995 ¹⁵¹ US	people ≥ 18 years self-reporting and status study	Oxford 194 Australia 194 CDC-88 97	?
Price 1992 ²¹⁴ US	people ≥ 18 years self-reporting	CDC-88 0.7	?
Primary care			
Wessely 1997 ³³⁶ UK	people 18-45 years self-reporting	CDC-94 2,600 [500] ^c Oxford 2,200 [700] ^c Australia 1,400 [200] ^c CDC-88 1,200 [100] ^c	minimal difference
Reyes 1997 ²²⁸ US	people ≥ 18 years diagnosis by physician	CDC-88 4-8.7	?
Buchwald 1995 ⁴³ US	age not given self-reporting and status study	CDC-88 75-267	minimal difference
McDonald 1993 ¹⁹³ UK	people 18-45 years diagnosis by physician	Oxford 2,480	3:1
Bates 1993 ²⁴ US	people ≥ 18 years self-reporting	Oxford 1,306 Australia 3,316 CDC-88 302	?
Gunn 1993 ¹²⁴ US	people ≥ 18 years diagnosis by physician	CDC-88 4.6-11.3	4:1
Ho-Yen 1991 ¹³⁸ UK	age not given diagnosis by physician	CDC-88 130	1.8 :1
Lloyd 1990 ¹⁷⁹ Australia	all ages diagnosis by physician	Australia 37.1	1.3 :1

^a see the original articles for 95%-confidence intervals

^b ? = not reported or study too small

^c after deduction for psychological comorbidity

4.1.2 *Who gets CFS?*

In most of the studies, female patients are in the majority, and they often account for as much as three quarters or more of the patients. Age-specific prevalence is highest between the ages of 40 and 49^{150,179,229,267}. The average age of onset of the symptoms in the different studies ranges from 29 to 35 years and the average duration of the symptoms is given as 3 to 9 years^{36,43,124,179,210,228,267,287,322,347}. CFS can also occur in young people and in those over 65 years of age.

4.1.3 *How many new cases are there?*

The two publications that have been published about the incidence of CFS give figures of 180²²⁹ and 370¹⁶⁹ per 100,000 population per year. These figures seem relatively high in relation to the stated prevalence figures. It is, however, inadvisable to draw a direct comparison between these incidence and prevalence figures since the methodologies followed in the studies vary and there are only two studies that give incidence figures.

4.1.4 *What is the clinical course?*

To build up a proper picture of the course and prognosis of CFS, one would need to question a group of patients annually for a number of years, starting from the diagnosis. No such research has been conducted. The available longitudinal research has only involved two measurements made at an interval of one to five years. Ten percent or fewer are found to spontaneously recover to such an extent that they regain their previous level of functioning^{36,204,210,287,297,322,347}. Evidence suggests that recovery or reduction of symptoms occurs more often in patients whose illness is of relatively short duration^{204,297}.

4.2 **Dutch data**

There is limited epidemiological data from Dutch patients. Table 4.2 gives a summary of the principal findings from studies involving more than 100 patients, which give some indication of the distinguishing characteristics of the Dutch CFS population. Three studies were primarily intended to determine the prevalence in primary healthcare. All but one³²⁴ of the studies mentioned were performed by the Nijmegen research team.

Table 4.2 Characteristics of the Dutch CFS patient population.

	Vercoulen1994 ³²¹	Bazelmans1997 ²⁷	Versluis1997 ³²⁴	Prins2001 ²¹⁵	Klein Rouweler1999 ^a	Van der Werf2002 ²⁹⁸
Year study performed	1990-1992	1993	1995	1996-1997	1998	1998
Characteristics of the study	written survey patients with self-diagnosis of CFS N= 395; response 90% usable 75%	written survey N=6657 response 60% usable 58%	GPs database 14 GPs 23,000 patients	518 consecutive patients in tertiary-care clinic for research purposes; 18-60 years usable and willing: 54%	written survey GPs N=1,000 response 71%	survey among supporters of Dutch ME Association N=7,050 response 37% usable 28%
Criteria	activity-limiting fatigue of unknown cause ≥ 1 year	activity-limiting fatigue of unknown cause ≥ 1 year; diagnosis made by GP	CDC-88	CDC-94 without the stipulation of the four symptom criteria	diagnosis made by GP	self-diagnosis and severe fatigue severe limitations ^b
Prevalence per 100,000	–	112	110	–	average 195 median 118 (confidence interval: 55-206) ^c	–
Patients per GP or practice	–	0 at 27% 1 at 23% 2 at 21% ≥3 at 29%	6.3 average per practice (distribution 4-11)	–	4.9 average per GP – (distribution 0-250)	–
Ratio :	3.0:1	4.3:1	6.3:1	3.8:1	4.3:1	5.7:1
Age data	18 to 73 years avg. 39 years	55% aged 25 - 44 years	avg. 38 years avg. 33 years	36.7 ± 10.1 years	92% older than 18 years	41.0 ± 11.8 years 5% older than 60 years 4% younger than 20 years

^a Klein Rouweler E., Bleijenberg G, Severens H. Research into prevalence of chronic fatigue syndrome as identified by general practitioners in the Netherlands and GPs' attitudes towards chronic fatigue syndrome. Internal report (in Dutch), Nijmegen University Hospital, October 1999.

^b operationalised as: VVV score > 20 and RAND-36 score < 65.

^c Calculated on the basis of the median and the inter-quartile range, owing to the highly skewed distribution.

4.2.1 *What is the incidence of CFS in the Netherlands?*

No research has been conducted among the general population of the Netherlands in which the CDC-94 case definition has been applied. For an estimate of the prevalence we are therefore reliant upon studies conducted among GPs that, moreover, have employed other definitions^{27,324} (and unpublished research by Klein Rouweler*) (see Table 4.2). These studies indicate a prevalence of 100 to 200 patients per 100,000 inhabitants (16,300 to 32,600** patients in the Netherlands). That prevalence is, however, lower than the lowest figure given in those international studies in which the CDC-94 definition has been applied and the diagnosis has been made by a physician, which is 235 per 100,000 (i.e. 38,300 patients in the Netherlands). The Committee therefore does not rule out the possibility that there may be between 30,000 and 40,000 CFS patients in the Netherlands, but it emphasises that this is conjecture (see 4.4). By way of comparison, there are around 13,000 patients with multiple sclerosis in the Netherlands, 18,400 with lung cancer, 23,300 with schizophrenia, 61,400 with epilepsy and 91,600 with breast cancer***.

4.2.2 *Who has CFS in the Netherlands?*

Between three and five times as many women as men have CFS. There are no detailed figures concerning the age of the patients, but the data that are available do not contradict the international findings.

4.2.3 *How many new cases are there in the Netherlands per year?*

The results of efforts made in Nijmegen to estimate this number vary so widely (2,900 – 9,800 new cases per year) that it is not possible to be certain.

4.2.4 *Dutch research into the clinical course of CFS*

The prognosis for CFS patients in the Netherlands has been investigated in three groups of patients with symptoms of varying duration. The results are summarised in Table 4.3.

* Klein Rouweler E., Bleijenberg G, Severens H. Research into prevalence of chronic fatigue syndrome as identified by general practitioners in the Netherlands and GPs' attitudes towards chronic fatigue syndrome. Internal report (in Dutch), Nijmegen University Hospital, October 1999.

** Number of inhabitants (8 November 2004) CBS (Statistics Netherlands) <http://www.cbs.nl/nl/cijfers/bevolkingsteller/popclocknl.asp>

*** Source: <http://www.rivm.nl/vtv/data/kompas/gezondheidstoestand/ziekte/prevalentie.htm> (20 December 2004)

Evidence suggests that the likelihood of recovery diminishes in direct proportion to the duration of illness.

4.3 Lack of data

There are no Dutch data concerning CFS in people of different ethnic origins. Nor has there been any research into a possible link between CFS and occupation.

The Committee has no means of comparing the incidence and prevalence in the Netherlands with that in neighbouring countries. No data are available about Belgium, France or Germany. The syndrome has only very recently begun to receive attention in Germany and the French-speaking regions. The situation in the UK is probably not much different from that in the Netherlands.

4.4 Scientific underpinning of the epidemiological data

The Committee finds the epidemiological data concerning CFS inadequate and inconsistent. The variation in the findings is enormous (Tables 4.1 and 4.2). This is mainly due to variations in the case definition and methodologies, including the degree of rigour that is applied in excluding other causes of fatigue. A weakness in the studies conducted among the general population is the fact that there has often been no clinical research conducted to confirm the diagnosis. Other sources of variation include the way in which the sample has been obtained and the number of people that have actually participated in relation to the size of the entire group that was approached.

The Committee emphasises the uncertainty that exists over the figures. This also means that the number of patients that is given in this chapter for the Netherlands is no more than a rough estimate. The Committee believes that epidemiological CFS research would benefit from the addition of a code for CFS to the International Classification of Primary Care (ICPC)*.

* <http://www.rivm.nl/> search for: ICPC

Table 4.3 Prognosis of CFS patients in the Netherlands.

	Vercoulen 1996 ³²²	Van der Werf2002 ²⁹⁷	Prins2001 ²¹⁵
Year study performed	1991-1992	1997-1998	1996-1997
Characteristics of the study	written survey 18 month interval t ₁ : N=298 t ₂ : N=246	interview 12 month interval N=79	control group in CBT study; 14 month interval t ₁ : N=88 t ₂ : N=76
Criteria	Oxford ²⁴⁹	CDC-94 ¹⁰⁹ or ICF duration ≤ 2 years	CDC-94 ¹⁰⁹ without the stipulation of four out of eight symptom criteria
Duration of the symptoms at t ₁	8.4 years (7.3 - 9.6 years)	1.4 years (6 – 24 months)	5.3 ± 5.4 years
Recovered	8 (3%)	6 (8%)	17-32% have improved (distribution depends on the measuring technique)
Improved	42 (17%)	30 (38%)	
Deteriorated or no change	196 (54%)	42 (80%)	

Possible causes and aetiology

‘The cause of CFS is unknown.’ This widely held contention is correct in the sense that the condition cannot be ascribed to a single viral, immunological, psychological or other factor. At the present stage of aetiological research, it is important to have good working hypotheses that fit in with the existing body of knowledge and take into account the experience of physicians and patients. In this chapter, the Committee outlines several strands of thinking that, given the current level of knowledge, are plausible and may point the way for treatment and scientific research.

5.1 Approach

Much of the research into the causes and aetiology of CFS is of mediocre quality. The groups that have been studied are frequently too small, control groups are missing or inadequate, or else there are other methodological shortcomings that undermine the conclusions. An additional deficiency in the aetiological research is the use of retrospective data. Patients relate where and how their symptoms began. Often this has been after a bout of flu or some other infection and, understandably, they attribute their symptoms to this. Thus, much of the research is (or has been) aimed at discovering an infectious cause. This approach has so far proved fruitless. It is known that people are especially susceptible to flu, colds and other infections at times when they are under pressure and also that these ailments have usually cleared up after a few weeks. The crucial question is therefore why some people fail to recover and precisely what happens then.

The systematic review approach is a good method for evaluating clinical interventions. However, the use of this approach during hypothesis-forming that reflects our current stage in thinking about the possible causes and aetiology of CFS¹²⁰ is of only limited usefulness and has only recently been adopted, to the degree that this has been possible²³³. Instead of adding an exhaustive new literature review to the never-ending stream of reviews and reports (some of them more systematic than others) about possible causes, the Committee outlines the contours of the picture that is beginning to emerge in the scientific literature. It includes not only the CFS literature, but also the neuroscientific and stress literature and the literature concerning unexplained physical symptoms. In addition, the Committee takes its own practical experience into consideration.

5.2 Body and mind

Physical and psychological causes of CFS are frequently considered as polar opposites in publications by patient organisations and other lay literature on CFS (and, in some cases, even in scientific articles). A constantly recurring theme – as was stated earlier – is the question of whether CFS should be regarded as a neurologic or a psychiatric disorder. The Committee finds this a spurious discussion. The neuroscientific research conducted in recent decades has clearly established that psychology (e.g. behaviour) and biology (e.g. biochemical processes) are, as it were, two sides of the same coin; they are two different methods of description. It is not a question of either one or the other, but of both together, and each influencing the other^{17,39,78,105,123,160,171,172}. The distinction between somatic factors on the one hand, and psychological and social factors on the other, is artificial, although it is sometimes necessary. This is not because these are separate issues but because this is how the respective scientific disciplines and the accompanying literature are divided up. The Committee's basic premise is therefore that body and mind form a single unity.

5.3 Why and how

Aetiology and pathophysiology are two aspects of the question as to what causes CFS. Whereas aetiology is, as it were, concerned with the 'why' (i.e. what circumstances make a person develop CFS?), pathophysiology is concerned with the 'how' (i.e. what biological disturbances are involved?). This distinction is seldom made in the literature. It is crucial, however, when it comes to sorting out the large body of data that vary in their level of abstraction and are derived from various fields of research, and translating findings into new hypotheses for research. Moreover, this approach provides a good

starting point for discussions with patients and opens up new possibilities for realistic and pragmatic healthcare provision.

5.4 Aetiology

There is growing support in the scientific world for distinguishing three categories of aetiological factors based on the moment at which they exert their influence^{6,141,243,273}.

- *Predisposing factors*: factors that determine differences between the susceptibility displayed by different people (i.e. why one person is more likely to develop CFS than another).
- *Precipitating factors*: circumstances that provoke CFS in susceptible individuals, also called triggers.
- *Perpetuating factors*: factors that cause the symptoms to persist and impede recovery.

The idea is that CFS only develops if predisposing, precipitating and perpetuating factors occur at the same time in one individual. Each of the three categories of factors is thus a necessary condition, but none of them is, in itself, sufficient to provoke CFS. The Committee provides below an (incomplete) overview of possible contributory factors for each category. As will become apparent, these factors are often closely related.

5.4.1 Predisposing factors

Familial factors: Research into families and twins indicates that CFS has familial aspects and that genetic makeup could be of relevance^{6,23,42,102,137,146,199,233,271,328}.

Sex: CFS is more often observed in women than in men (Chapter 4).

Learning history: What people experience in their youth (the ‘learning history’) has a major bearing on their later life. People with unpleasant experiences in their youth – such as neglect, violence or abuse, serious illness (affecting either themselves or close family members) or other traumas – seem more susceptible than other individuals. It is known that traumatic events in early childhood result in greater sensitivity to stress factors later in life^{8,46,62,65,67,93,98,125,190,231,279,281,282,312,314}. The connection with CFS requires further investigation.

Personality: There is evidence to suggest that a neurotic disposition (a tendency towards exaggerated carefulness, fear of failure, an inability to say ‘no’ and to relax) lead to chronically elevated stress levels. This could make people more susceptible to CFS^{15,98,125,140,221,222,277,312}.

Lifestyle: Particular lifestyles that are related to personality (e.g. a compulsion to achieve or an obsessive striving for control and perfection), can give rise to chronic stress. CFS patients often report having led an overactive life (e.g. extreme overwork or excessive engagement in sports – lifestyles that are a source of chronic stress) before they developed the illness^{22,140,178,311-313,315,316}.

Lack of physical activity: People who have previously led a life with little physical exercise are at greater risk of developing CFS after glandular fever (mononucleosis)^{44,59,155,343}. There is also evidence to suggest that a lack of physical exercise in youth increases the risk of CFS later in life^{325,342}.

5.4.2 *Precipitating factors*

Acute physical stress: Serious injuries, chronic sleep disturbances, an invasive surgical procedure, or pregnancy and childbirth can precipitate CFS^{190,237}. This aspect has yet to be fully investigated. However, a great deal of research has been conducted into the role that infections play in the development of CFS, particularly because three quarters of patients indicate that the symptoms started with an infection^{81,237}. The following is a summary of the findings:

- Epstein-Barr virus (mononucleosis, glandular fever). Fatigue is the hallmark symptom during the acute phase. This is the only type of infection for which a causal relationship has been demonstrated with fatigue of more than 6 months duration^{6,44,178,233,340,343}. In point of fact, only a few patients with glandular fever subsequently develop CFS. Although the virus persists in the cells of people who have experienced the infection after recovery, there is no demonstrable difference between viral activity and immune response to the virus in people who subsequently develop CFS and those who do not^{274,275}.
- *Everyday infections (respiratory infections, flu):* Quite a few patients report that the symptoms began after a respiratory infection (colds, flu) or an intestinal infection.
- *Other infections:* A relatively high percentage of chronic fatigue is observed after specific infections (e.g. hepatitis C virus^{164,178}, Q fever^{131,178,346} and Lyme disease^{117,178,264}).

Acute psychological stress: Major life events, such as the death of a loved one or being left by a partner, can precipitate CFS, as can other emotionally stressful events or situations (whether or not work-related), such as the feeling of being unable to live up to other people's expectations^{130,237,284}. Special mention needs to be made in this connection of the unexplained physical symptoms that can occur in the aftermath of both armed

conflict and peace missions, as well as after major disasters²⁶¹. Though these symptoms are in some respects dissimilar to CFS, they also display marked similarities.

5.4.3 *Perpetuating factors*

Physical inactivity: Lack of exercise may play a key role in perpetuating the symptoms. This has, in any event, been conclusively demonstrated in the case of CFS following glandular fever^{48,111,155,341,343}.

Periodic overactivity: As soon as they start to feel well again, CFS patients often have a tendency to take on too much, resulting in extreme fatigue, an increasing feeling of malaise and pain, and difficulty in recovering.

Perceptions of the disorder: Many CFS patients ascribe their symptoms to strictly physical causes. Somatic attributions lead to avoidance of physical activity and frequent visits to the physician. The symptoms are exacerbated by the idea that patients themselves have no control over them. There is strong evidence to suggest that attitudes of this kind impede recovery^{6,22,26,46,54,76,126,134,233,248,252,276,323}.

Increased attention to physical sensations: When confronted with situations that place them under great pressure, individuals can develop a form of hypersensitivity to physical sensations that is known as somatic hypervigilance. Physiological signals that one would normally ignore are then interpreted as threatening^{22,77,98,99,125}. This can have the effect of exacerbating fatigue symptoms and lead to behaviour that perpetuates limitations^{6,22,77,123,142,239,323}.

Behaviour of care providers: There is evidence that the approach adopted by the physician influences the development of CFS. Over-attention to the somatic dimension (e.g. excessively frequent physical examinations) or to the psychological dimension (e.g. repeatedly emphasising psychological causes) can lead patients to feel unrecognised and unacknowledged. Moreover, a lack of understanding and communication skills on the part of the physician, which prevents him from providing the patient with an acceptable explanation, can give rise to misconceptions about the condition. The same applies when the patient receives conflicting messages from different care providers^{22,32,46,74,190,206,265,266}.

Social factors: People around the patient may reinforce his role as an invalid by encouraging sickness behaviour and affirming dysfunctional views^{38,47,197}. It is quite feasible

that anecdotal information in the popular press and on the internet (and certain information from patient organisations) may have a similar effect.

Being ill brings with it a different rhythm of life. Alongside the undeniable disadvantages, it can also sometimes have advantages. This applies not only to CFS, but to being ill in general. In some cases, these advantages may unintentionally impede recovery. The advantages may include such things as being looked after, getting extra attention, and being free from obligations and responsibilities that are associated with going to school, studying, working or performing household tasks. Until recently, for example, people who started receiving benefits under the Sickness Benefits Act (ZW) or the national disability insurance (WAO) scheme could continue to do so for years on end without their fitness for work being periodically assessed. Once they have become accustomed to this rhythm of life, patients often find it difficult to revert to a situation in which they are once again subject to responsibilities and obligations^{22,38,47,48,65,67,233,239,265,280,311}.

5.4.4 *Remark: Chronic infections are not a perpetuating factor*

Many patients report increased sensitivity to infections and believe that they enter a downward spiral on account of these persistent infections. Many hypotheses have been advanced about the role of infections as a perpetuating factor for CFS. Micro-organisms are claimed to persist after an infection and elicit an abnormal immune response. Over the years, various persistent micro-organisms have been proclaimed by researchers – often with a great deal of publicity – as the cause (or at least a key contributory factor) of CFS. Examples include the Epstein Barr virus, cytomegalovirus, human herpes virus 6, Borna disease virus, retroviruses, Mycoplasma species (e.g. *M. fermentans*), *Coxiella burnetii* (the causative agent of Q fever), various strains of *Borrelia* (the causative agents of Lyme disease), *Helicobacter pylori*, various strains of *Brucella* and *Candida*, and *Toxoplasma gondii*. None of these micro-organisms have been conclusively shown to be a perpetuating factor for CFS. The contention that CFS is associated with increased susceptibility to infection has proved untenable^{96,100,156,164,178,233}. The hypothesis that a dysregulation of the Rnase L route (2-5A synthetase) plays a role in the pathogenesis is disputed^{85,122,202}.

5.5 Pathophysiology

Numerous hypotheses have been advanced over the years with regard to the underlying biological mechanisms of CFS. Besides persistent viral infections or a disturbance of the immune system or antiviral mechanisms, some people have placed particular emphasis on disruption of neurohormonal systems, such as the HPA axis and the autonomic ner-

vous system. These hypotheses usually focus on one particular aspect of the disorder and not on the entire spectrum of signs and symptoms. This approach has not proved to be productive.

Here the Committee presents a model that fits in both with the symptomology (3.1), as well as the aetiology, of CFS (5.4).

5.5.1 *Unexplained physical illnesses*

CFS is one of the many syndromes characterised by unexplained physical symptoms. As explained in Chapter 3, terms such as CFS, fibromyalgia and IBS satisfy the need for a specific diagnosis within a particular medical speciality. Such a distinction may well be meaningful for the symptomatic treatment of the patients, but it is questionable whether it advances the research into the pathophysiology of these conditions³³⁹. That research has hitherto chiefly concentrated on those areas in which one syndrome differs from another. Given the conspicuous overlap between the syndromes, it seems logical to focus attention not only on the differences between the syndromes but also on their similarities^{22,93,290,311,312}. Although ‘functional somatic syndromes’^{22,338} may be a useful collective term for this group of conditions, it does not advance our understanding of the pathophysiology, particularly because this implies that these are symptoms without a biological foundation. This is inconsistent with the findings of recent neurobiological research and does not provide a fruitful point of departure for clinical practice^{244,351}.

5.5.2 *Stress, hormones and the immune system*

Although little is known with any certainty about the pathophysiology of unexplained physical illnesses (including CFS), the Committee points out a number of promising explanatory models provided by the modern neurosciences. The relevance of these models to CFS is still uncertain, but the Committee considers it worthwhile to discuss them here since they afford an opportunity to bridge the gulf between the somatic and the psychological, and they provide a sound basis for scientific research.

Chrousos and Gold studied the pathogenic consequences of both hyperactivity and hypoactivity of the hypothalamic-pituitary-adrenal axis (HPA axis)^{66,121,289}. The central hormone, cortisol, is not only essential for the control of various physiological processes such as the energy metabolism, but also plays a major role in emotional well-being and the cognitive assessment and evaluation of situations^{60,94,207}. Research has meanwhile indicated the likelihood that disruption of receptors may occur at various levels after a period of chronic stress (i.e. hyperfunction of the HPA axis), leading to hypofunction and hyporeactivity of the entire system^{63,94,121,194-196,350}. It is claimed that the ability to cope with physical and mental stress is impaired from that moment on. Discrete disor-

ders of the HPA axis (a deficiency of corticosteroids in combination with an overproduction of ACTH⁴⁰) have been described in patients with CFS^{40,69,70,72,94,112,230}.

The HPA axis has an important role in the regulation of the immune system. An infection with a virus or bacterium (or tissue damage caused by an accident or operation) usually results in activation of the immune system. A reaction occurs at the affected site (respiratory tracts, gastrointestinal system, etc.), leading to the elimination of the infecting micro-organism and recovery from the local injury. Animal studies have shown that chemical signals are then also sent to the brain, which subsequently also begin to release cytokines there²¹⁸. These substances induce so-called ‘sickness behaviour’^{159,161,165,326} – a condition characterised by a tendency to withdraw from social contacts, listlessness, somnolence, impaired concentration and memory, reduced appetite, mild fever and increased sensitivity to pain and pressure³³¹. People who have been administered particular cytokines (IFN- α) for research purposes have, indeed, been found to display sickness behaviour⁴⁹.

Hitherto, the majority of research has focused on disruptions of the HPA axis. Disruption of other neuroendocrine systems – e.g. the sympathetic nervous system (with noradrenaline and adrenaline) and the dopaminergic system – can also be anticipated. These systems are, after all, interconnected: disruptions in one system bring about changes in another. In young CFS patients, for example, an increased level of adrenaline has been detected in the blood, which suggests a disruption of the sympathetic nervous system. The cells of the immune system have also been found to respond less well to adrenaline in these patients. The inhibitory effect of the sympathetic nervous system, which is especially necessary during stress and infections, appears to have decreased. Persistent disruption of the neuroendocrine system may ultimately cause the immune system to lose its sensitivity to neuroendocrine regulation^{157,207}. In such circumstances, any additional stress (after moderate physical exertion, for example) may result in abnormal immune activation together with the attendant sickness behaviour, even in the absence of infection or tissue damage^{184,331}.

A further valuable model is provided by Ursin and Eriksen. According to these researchers, psychobiological sensitisation mechanisms underlie several unexplained physical symptoms, including fibromyalgia and CFS. In situations of chronic stress, particular centres in the brain (especially in the limbic system) are said to become increasingly sensitised to stimuli^{97-99,290-292}. This results in ‘harmless’ signals from the environment and from one’s own body being interpreted as signs of danger (hypervigilance). Furthermore, the higher, conscious centres of the brain, which usually inhibit the limbic system, are said to lose control and ultimately even play a part in worsening symptoms by initiating avoidance behaviour: the patient refrains from physical exertion in order to avoid pain and fatigue¹²⁵. This ties in with the finding that perception is impaired in patients

with CFS. Psychological research has revealed that patients' perception of their cognitive abilities do not match their actual performance: they believe they have performed worse than the test result indicates^{183,320}. A similar situation appears to arise with regard to patients' perceptions of their own exercise tolerance^{25,68}. Sleep disturbances can also be perceptually determined³³³. Functional MRI research reveals that different brain areas are activated in patients with CFS than in healthy controls when they are instructed to perform simple tasks⁸⁴. These hypotheses and findings promote a better understanding of the effects of cognitive behavioural therapy (CBT, Chapter 6). After all, a key element in this process is the desire to bring about changes in the patient's perception of physiological signals.

5.5.3 *Stress-related pain and exhaustion syndromes*

The pattern of symptoms associated with unexplained physical illnesses appears to suggest a disruption of control systems (or of communication between control systems), in which the central nervous system, the hormonal system and the immune system are all implicated⁵⁸. It is rare to encounter marked deviations in individual parameters. This disruption appears to have its origins in the same basic pattern: a long-term and serious disturbance of the balance between emotional endurance and stress, which in time causes an imbalance of various homeostatic mechanisms (e.g. energy balance, recovery processes and sensitivity to pain). In other words, CFS, fibromyalgia and associated syndromes can be regarded as stress-related pain and exhaustion syndromes³¹¹.

It seems likely that persistent, non-adaptive changes in the brain's cytokine balance may occur in susceptible individuals as a result of an episode of severe and prolonged stress⁵⁷. This susceptibility may be genetically determined^{23,135,221} and stressful experiences in early childhood (or subsequent physically or psychologically stressful factors) may be implicated (5.4.1). There is as yet no conclusive evidence of cytokine abnormalities in CFS patients¹⁸². Nevertheless, the hypothesis of a change in cytokine balance in these syndromes merits closer investigation because it fits in so well with the profound feeling of malaise that predominates in many patients (more so even than fatigue) and with the abnormal sensitivity to pain that can manifest in muscles, joints and in the gastro-intestinal system.

5.6 **Prospects for the future**

CFS cannot be dismissed as a condition that is exclusively caused by psychological factors. The pathophysiological model discussed here effectively fleshes out the term biopsychosocial. It provides a multidimensional and flexible insight into CFS, thereby taking

into account biological *and* psychosocial factors. Furthermore, this concept obviates the need for dualistic divisions into 'neurologic' ME and 'psychiatric' CFS.

5.6.1 *Primary prevention*

There is, to date, absolutely no scientifically validated knowledge concerning the prevention of CFS. The model presented for the aetiology and pathophysiology of CFS demonstrates how extremely important it is to monitor the balance between stress and physical capacity.

5.6.2 *Secondary prevention and treatment*

Stress is a universally recognisable concept that serves as a plausible pathological interpretation of CFS and, in turn, encourages self-sufficiency and self-care. This concept provides specific pointers with regard to secondary prevention and treatment. In the consulting rooms of GPs and occupational physicians, it justifies a management programme that focuses on monitoring the balance between rest and activity. The model also provides a basis for explaining the effects of cognitive behavioural therapy and progressive improvement of fitness to patients, and thus motivating them to undergo these therapies.

5.6.3 *Scientific research*

Although the concept of stress may well be recognisable, this does not alter the fact that it is a complex phenomenon that has not been unequivocally defined. Psychological stress research frequently fails to take sufficient account of changing perceptual aspects and subjective psychological stressors (e.g. anxious expectations). New, more sophisticated and longitudinal research strategies (see Van Praag³¹⁸, for example) are possibly more suitable for research into the role that stress plays in CFS.

Perceptual disorders almost certainly play a role in CFS. Research into the nature of these disorders and the role of psychobiological sensitisation mechanisms in their development may shed fresh light on the development of CFS and other unexplained physical illnesses.

A great deal more neuroscientific research will need to be conducted before an overall picture can be formed of neuroendocrine disruption and the implications for the immune system. Cleare pointed out the numerous possible pitfalls involved as far as research in the research into the HPA axis in CFS patients is concerned⁷⁰. A multidimensional endocrinological approach is required in order to rule out the influence of confounding factors within the complex interactions of the system. Furthermore, the author recommends that prospective research be conducted in patients at increased risk of CFS

(e.g. following Epstein-Barr viral infection or an invasive surgical procedure). Research into neurobiological changes in patients who recover may also provide valuable information^{71,72}.

The concept of stress also opens up interesting possibilities for pharmacotherapeutic research. These include the development of agonists and antagonists for hormones from the HPA axis, the dopaminergic system and the sympathetic nervous system that can correct disruptions of the system²⁸⁹ and substances that block cytokine receptors and should therefore be capable of reducing the symptoms of sickness behaviour^{330,332}. Compounds of this kind would be a welcome addition to the present arsenal of CBT-oriented and rehabilitation-oriented strategies.

Finally, the pathophysiological model discussed here is overarching and unifying in character. Besides CFS, it also provides an excellent basis for the study of other unexplained physical illnesses. In fact, it affords sufficient scope for the identification of subgroups. It is, after all, important to investigate why it is that the concrete pattern of symptoms associated with these disorders is so variable. A case in point is research into the interaction between genetic susceptibility and (physical and psychosocial) environmental factors, and likewise into psychological and social determinants of symptom perception and sickness behaviour.

Diagnosis, support and treatment

6.1 About fatigue

Fatigue is a normal, everyday phenomenon. It is no more than a signal that it is time to take a break. In two recent Dutch studies, 40% of the participants – one third of the men and around half of the women – were fatigued in the two weeks preceding the survey^{29,234}. The figures from abroad are comparable^{86,233}.

Fatigue is a term with many nuances. Being weary, tiring quickly during exercise, exhaustion, feeling ill and general malaise are all forms of fatigue. There is no all-embracing definition. For clinical purposes, fatigue is defined as difficulty initiating or maintaining voluntary activities⁵⁸. Fatigue is a state of mind. The way it is perceived is subjective: only the person in question can determine the presence or absence of fatigue. Fatigue is an extremely non-specific symptom: it has a wide variety of physical, psychological and social causes, ranging from a normal reaction to an active lifestyle or a major event to illnesses such as depression, cardiovascular diseases or cancer.

Diagnostic and scientific research into fatigue symptoms is complicated by the many gradations of fatigue, its subjective nature, and the fact that it can form part of a variety of circumstances and disorders.

6.2 Some statistics concerning fatigue in general practice

The fact that fatigue is a very common symptom in general practice is amply demonstrated in the *Second National Study of Illness and Procedures in General Practice*²⁹³.

Recent research* based on this study contains a wealth of data on fatigue in general practice, some of which are outlined below.

Research conducted among the general population showed that 36% of the interviewees had felt tired in the past two weeks and that 6.1% had consulted their GP for this symptom. Of this group, 5.6% still had fatigue (for which they consulted their GP) three months later. For 2.5%, this still applied after six months. Referral within primary care took place in 8.5% of cases, with referral to secondary care in 15%. For a standard general practice (2,350 patients), these data mean that \pm 66 patients visit a GP with fatigue every year, for \pm 4 of them the fatigue lasts three months or longer, and for 2–3 it lasts six months or longer. In each practice, 5–6 patients are referred annually within primary care and \pm 10 patients receive a referral to secondary care. Of the group who consult a GP with fatigue symptoms, one third are men and two thirds are women.

6.3 Key points in the management of fatigue symptoms**

Fatigue is regularly cited in the Netherlands Society of General Medical Practitioners (NHG) Standards (guidelines for GPs) as a symptom of all manner of illnesses and disorders. There is, however, no standard for the management of patients with ‘fatigue’ as their primary symptom. This is not particularly surprising, since fatigue gives the GP little to go on when making a diagnosis. According to the Committee, however, there are now sufficient pointers to permit the formulation of a guideline for the management of fatigue symptoms, which can include unexplained fatigue symptoms (and, in particular, CFS and its possible prevention)^{86,233,248,296}.

6.3.1 General points

There is evidence to suggest that the physician’s actions influence the outcome, especially in the case of non-specific symptoms (2.4, 2.5, 5.4.3). The affective dimension of the physician’s actions therefore requires special attention^{198,248}. Points that warrant careful consideration are:

- investment in establishing a good relationship with the patient
- taking the symptoms and the patient seriously
- allowing patients to express their emotions
- explaining the different factors that can play a role in fatigue.

* Cardol M, Bensing J, Verhaak P, de Bakker D. Moeheid: determinanten, beloop en zorg – onderzoek op basis van gegevens uit de *Tweede Nationale studie naar ziekten en verrichtingen in de huisartsenpraktijk* [Fatigue: Determinants, Course and Care – Study Based on Data from the *Second National Study of Illness and Procedures in General Practice*]. Utrecht: NIVEL; preliminary version, 20 December 2004. NIVEL will publish the report in 2005.

** See Chapter 7 for additional points to consider in relation to children.

It is important to tell patients that fatigue may well be a signal to take things easier, but that total rest can have adverse long-term effects. The best advice for patients is that they must do whatever they still can, if necessary after having (temporarily) adjusted their work or working hours in consultation with the occupational physician, or – if the patient is unemployed – other members of the household^{48,297}. The GP will always need to explicitly discuss the subject of work.

Patients with possible CFS who consult their GP present with severe fatigue or exhaustion, possibly combined with other non-specific symptoms such as headache, sleeping badly, and a flu-like feeling. Some people will visit their physician with these symptoms at an early stage and have no preconceptions as to a diagnosis. Other patients will consult the GP (sometimes only after several months have elapsed) convinced that they have ME or CFS, whereas it has not yet been established whether there is another disorder that might explain their condition^{245,294,295}. There are also patients whose fatigue has an obvious initial explanation (e.g. glandular fever or a serious operation). The point of departure when determining the stage of the patient's illness is always the onset of the symptoms and limitations.

6.3.2 *The acute phase*

The period up to one month after the onset of the symptoms is known as the acute phase²⁹⁶. The GP takes the history and investigates whether there is an 'everyday' explanation for the fatigue, such as mental or physical stress, other forms of stress (problems, life events), a viral infection or some other somatic disorder. Exploring the background to the request for help is an important element in the initial consultation for patients whose primary symptom is fatigue. Particular aspects to be considered include

- thoughts: what does the patient himself think about the reason or underlying cause?
- perceptions: how inconvenient is the condition?
- consequences: how burdensome is the condition for the patient and what can he no longer do?
- expectations: what does the patient expect of the GP?

The answers to these questions will frequently indicate which points the physician needs to consider. A limited physical examination may be appropriate, but if a great deal of time has been spent on the discussion, this can also wait until a subsequent consultation. If the physician has nothing specific to go on, then it is prudent to point out that fatigue is usually a benign and transient condition, and to give advice on a healthy lifestyle (eating, drinking, exercise, relaxation, sleep, work). The GP asks the patient to come back if the situation has not markedly improved in four to six weeks' time.

6.3.3 *The subacute phase*

The subacute phase lasts for up to six months after the onset of the symptoms²⁹⁶. Only a small proportion of patients reach this phase. The emphasis in this phase is on ruling out a specific cause. The GP repeats the history-taking process, performs a careful physical examination and attempts once again to shed light on the background to the patient's request for help. If this fails to provide any specific clues, then he proposes two additional avenues of investigation:

- physical: limited laboratory tests, in accordance with the NHG Standards for Blood Testing²⁰⁰
- psychosocial: an exploratory history of cognitive, emotional, behavioural and social aspects, taking account of possible stress factors; it may be helpful to have the patient keep a (structured) diary.

If this fails to produce anything specific, then it is important to once again carefully consider the patient's own perception of his fatigue and his concerns, and to repeat the advice with regard to a healthy lifestyle. The GP asks the patient to come back if the situation has not improved markedly (in total) in three months.

If there has been little change in the pattern of symptoms after three months, then the GP explains that there is little likelihood of the fatigue being caused by a serious illness. He then explains that it is most probably a benign form of fatigue that will clear up of its own accord. Unless there are specific problems, practitioners should be wary of referring patients to a specialist (physician, neurologist, psychiatrist)^{30,58}. In some cases, however, a referral may be appropriate in order to reassure the patient and those around him. Pending the specialist examination, the patient's attention is once again drawn to the benefits of physical activities and the need to stay in circulation. The GP once again carefully considers the patient's perception of the fatigue and explains that extra rest and concern will not ease the fatigue. A patient diary may prove beneficial here too, since it will pave the way for a discussion about other ways of coping with the symptoms.

6.3.4 *The chronic phase*

If there has been no change in the symptoms after six months and further investigations have proved fruitless, then the patient can be said to have chronic fatigue of uncertain aetiology. The diagnosis of CFS will apply if extreme fatigue that imposes considerable limitations on the patient's daily functioning persists for at least six months without any obvious explanation. Questionnaires are available for determining the severity of the fatigue and functional invalidity^{7,306}. Furthermore, in order for fatigue to be diagnosed

as CFS according to the CDC-94 definition, it must be accompanied by four of the eight defined additional symptom criteria (Chapter 3). If the patient does not satisfy all of these criteria, then the physician should precisely explain why this is so. This has not hitherto been considered relevant to the further management of the patient.

Patients usually have great difficulty accepting the news that no specific cause has been found for their symptoms and that there is no point in continuing to look for this. This discussion is, therefore, not an easy one. The physician may find that the stress concept discussed in Chapter 5 provides a framework for this conversation.

6.4 Fatigue symptoms and CFS in relation to work

It is not only GPs, but also occupational and insurance physicians, who encounter patients with fatigue symptoms and CFS (the occupational physician in the first two years of the patient's illness and the insurance physician thereafter). The points to consider in relation to patient management (6.3) are no less important for them¹⁶⁸, but there is a difference of emphasis. Whereas the key concern for occupational physicians is the patient's return to work, for the insurance physicians it is the assessment of his entitlement to social security benefit. Thus the approaches adopted by occupational and insurance physicians are not precisely the same, but the key issue for both is identical: is the client sick? – and if so, what are the obstacles that prevent him from working and what is the cause of these?

6.4.1 Assessing fitness for work

There is a very common misconception that a diagnosis entitles a person to absence from work or to receive social security benefit. This misunderstanding can be cleared up by explaining to patients that manifestations and consequences of illness are what matters, not causes. The key question is whether an individual is able to function at work, in spite of their disease or infirmity, and if so, to what extent. A medical diagnosis is not a sufficient condition for judging whether someone is fit for work^{1,163}. The guidelines established in the *International Classification of Functioning, Disability and Health*³⁴⁸ provide a framework for occupational and insurance physicians (ICF, Annex C). Furthermore, the statutory framework – the so-called *Schattingsbesluit* (Assessment Decree) – is determinative in the practice of insurance medicine^{1,2}. Assessment of fitness for work is based on the following three 'pillars':

General functioning: Someone who cannot, generally speaking, function owing to disease or infirmity is also unable to work. If, however, he is able to function to some extent, then certain forms of work will also soon be possible. What is important is to

ascertain what limitations the person in question experiences in his work and what solutions there are that would enable him to work¹⁶⁸. This gives a broad picture of the global conditions under which he would be able to get back to work. The mere fact that someone is unable to cope with his work is not a reason to conclude that his inability to work is attributable to illness^{168,317}. There are, after all, other reasons – both concerning working conditions and social circumstances – that might make it impossible for someone to work.

Consistency: There must be a logical and consistent relationship between illness, limitations and a decline in work participation. If this is not the case, then incapacity for work cannot be attributed to illness. The complaints that clients express about their health and about the decline they have experienced in their functional abilities form the starting point for the assessment. The actual existence of these symptoms and the client's ability to function are then tested. Limitations are considered at three levels: impairments, activity limitations and participation restrictions³⁴⁸ (Annex C). It is important to realise that disorders at the physical level are not automatically accompanied by limitations in the performance of activities and that there is not always an obvious relationship between limitations and an identified disorder. Explanation and openness about this approach is a prerequisite for a good relationship with the patient.

Multifactorial problem analysis: Careful problem analysis, with particular attention to the social context, is first of importance in order to provide proper support to sick employees. Second, such an analysis plays an essential role when the insurance physician is forming an opinion about entitlement to social security benefit as a result of illness. After all, there may conceivably also be other factors, apart from illness, that prevent the individual concerned from working but that do not confer any entitlement to social security benefit. It is the job of the insurance physician to ascertain why someone is unable to work.

It is necessary to be open with the patient in these matters, however difficult that might be in practice.

6.4.2 *Resumption of work*

Restoration of functioning – not rest – is the key to the recovery process. The motto of occupational physicians and GPs alike must be: 'To stand still is to move back'. Rest by itself may reinforce any tendency that the patient may have to avoid problematic situations and thereby prolong sick leave and set in motion a process of social marginalisation³⁵. Consequently, the return to work does not have to wait until the

patient is completely free of symptoms. This demands a step-by-step approach and, if necessary, adjustment of the work in consultation with the employer¹⁶⁸. It is important that the patient should recognise his situation, including his symptoms and limitations, and actively address it, so that he can gradually optimise his functioning without over-taxing himself. Just because someone is (temporarily) unfit to perform his job does not mean that he is totally unfit for work forever after.

6.4.3 Problems

Good cooperation between GPs and occupational and insurance physicians takes some time to achieve^{18,133}. This cooperation is essential, because GPs usually know more about the patient's background, and occupational and insurance physicians specialise in identifying the illness-induced limitations that are preventing the patient from working. It is important that the patient is managed in a cohesive manner and that he receives the same message from all of the involved physicians.

In practice, adjustment of work or working hours is something of a stumbling block. As a result, the necessary step-by-step approach to the resumption of work does not always live up to its promise.

Knowledge about the effectiveness and efficiency of reintegration measures and activities, and the accompanying support and treatment regimes, are almost completely lacking. Research in this area is desirable.

6.5 Treatment options

The aim of treatment is to improve quality of life and to reduce fatigue and secondary symptoms. All manner of treatments are available for CFS (see the internet), but few of them have been scientifically tested for effectiveness.

Table 6.1 provides a summary, taken from *Clinical Evidence*^{227,*}, of treatment modalities that have been reviewed. The message is clear: only cognitive behavioural therapy (CBT) and graded exercise training (GET) have been demonstrated to be effective for patients with CFS.

* *Clinical Evidence* is a *British Medical Journal* publication and the pre-eminent source of information for the medical profession. It provides up-to-date reviews of the efficacy of treatments for diseases and disorders. A hard copy is annually published.

Table 6.1 Treatments for patients with CFS. Source: *Clinical Evidence*²²⁷.

BENEFICIAL

Cognitive behavioural therapy (CBT):

- One systematic review found that CBT administered by highly skilled therapists in specialist centres improved quality of life and physical functioning compared with standard medical care or relaxation therapy.
- One additional multi-centre RCT found that CBT administered by less experienced therapists may also be effective compared with guided support groups or no interventions.

Graded exercise training (GET):

- Graded aerobic exercise RCTs found that GET improved measures of fatigue and physical functioning compared with flexibility and relaxation training or general advice.
- One RCT found that an educational package to encourage graded exercise improved measures of physical functioning, fatigue, mood, and sleep at 1 year compared with written information alone.

UNKNOWN EFFECTIVENESS

Dietary supplements:

- One small RCT found no significant difference between a nutritional supplement (containing multivitamins, minerals, and co-enzymes) and placebo in fatigue severity or functional impairment at 10 weeks.

Evening primrose oil:

- One small RCT found no significant difference between evening primrose oil and placebo in depression scores at 3 months.

Magnesium (intramuscular):

- One small RCT found that intramuscular magnesium injections improved symptoms at 6 weeks compared with placebo.

Antidepressants; corticosteroids; oral nicotinamide adenine dinucleotide:

- RCTs provided insufficient evidence about the effects of these interventions in people with chronic fatigue syndrome.

UNLIKELY TO BE BENEFICIAL

Immunotherapy

- Small RCTs provided limited evidence that immunoglobulin G modestly improved physical functioning and fatigue at 3–6 months compared with placebo, but it was associated with considerable adverse effects.
- Small RCTs provided insufficient evidence on the effects of interferon alfa or acyclovir compared with placebo.
- One RCT found that staphylococcus toxoid improved symptoms at six months compared with placebo, although it is associated with local reaction and could cause anaphylaxis.

Prolonged rest

- We found no RCTs on the effects of prolonged rest. Indirect observational evidence in healthy volunteers and in people recovering from a viral illness suggests that prolonged rest may perpetuate or worsen fatigue and symptoms.
-

6.5.1 Cognitive behavioural therapy (CBT)

CBT is a form of psychotherapy that aims to bring about changes in patients' cognitions and behaviours. This technique has proved effective for a series of disorders, including

depression, panic disorder, obsessive-compulsive anxiety disorder, abdominal discomfort and various other unexplained physical symptoms^{33,132,167,181,201,263,302}. It is essential to direct the therapy at cognitions and behaviours that belong to the disorder in question. Thus, the content of a CBT programme for one disorder will differ from that for another.

CBT has now been practised in CFS patients for around ten years in several places in the world. Success was modest at first^{108,180}, but its effectiveness has gradually increased^{87,110,212,246}. CBT invariably emerges as an effective therapy in systematic reviews of interventions for CFS^{225-227,345}. This treatment is successful to some degree in around 70% of patients.

There has been no recorded case to date of deterioration as a result of CBT, nor would such deterioration be consistent with clinical experience. The effect of CBT is lasting, as studies among CFS patients who had undergone CBT five years earlier have now revealed^{88,213}.

6.5.2 *Graded exercise training*

An essential element in all effective forms of CBT for CFS is attention to the structure of physical activities. Thus, it is artificial to view CBT and GET separately. Whether GET is, in fact, effective in treating CFS without any form of CBT has yet to be properly investigated. A large study is due to start shortly in the UK into the effectiveness of GET including CBT, GET without CBT, and ‘pacing’. Pacing is a form of controlled exercise that is advocated by patient organisations. The difference between this and GET is that the patients themselves define the limits of their activity levels.

6.5.3 *Dutch experiences with CBT*

The Nijmegen Expertise Centre for Chronic Fatigue (NKCVC) has developed a treatment protocol that is based on the perpetuating cognitive and behavioural factors from the aetiological model that was discussed in section 5.4^{33,34,134,323,337}. The main points are the ‘restructuring’ of dysfunctional ideas and behaviour, and controlled exercise. The protocol has been tested in a multicentre randomised study²¹⁵. CBT brought about a greater reduction in fatigue and limitations than did conventional medical support or self-help groups led by a social worker. Closer investigation revealed that CBT was not successful in patients with a pervasively passive activity pattern and in patients who were involved in an appeal procedure. The latter group is consequently excluded from CBT while such a procedure is in progress. There is a modified protocol for patients with a pervasively passive activity pattern that has proved effective (at least, in young people).

It appears to be important that the therapy be tailored to it the individual. CBT in the form of group therapy has been found not to be suitable for every patient. Indeed, it has been suggested that CBT is no more than a means of coping better with the symptoms. The treatment goal in Nijmegen, however, is recovery and a return to work: the therapy is considered to have been successful when the patient no longer regards himself as a patient³³. Research will need to show whether recovery (as formulated by this definition) is accompanied by neurobiological changes. Cleare provided an initial clue in demonstrating that changes can occur in the HPA axis under the influence of CBT⁷¹.

It is important to make the patient realise that the aim is that he should feel healthy again, but also that this does not always mean that he should become 'his old self'. Some people will regard this as a loss with which they have to come to terms. Care-givers and GPs should watch out for this.

Self-sufficiency is an important aspect. The patient must not undergo any other medical examinations or treatments for CFS during CBT because he needs to be able to attribute improvements to his own behaviour. Furthermore, he cannot, for the time being, expect to receive assistance with such things as taxi fares and applications for services and facilities (e.g. a stairlift or electric mobility scooter), since these are incompatible with the objectives of CBT. It is extremely important to motivate patients to undergo therapy.

CFS patients are a highly diverse group. It is therefore desirable that research should be conducted into additional, less intensive variants of CBT and the indication for these. Therapy will be more efficient if its intensity is properly matched to the needs of the individual patient.

Not all CFS patients are equally enthusiastic about undertaking CBT*. This opposition hinges on the idea that this form of therapy is based on the premise that CFS is 'in the mind' – an idea that has been sufficiently refuted in all previous chapters. It is worth bearing in mind that CBT is not a panacea. It is an intensive form of therapy that asks a great deal of the patient and it is not always successful.

6.6 The care of CFS patients

6.6.1 Guidelines

The general practitioner is the central figure in the diagnosis and support of CFS patients. However, some GPs are better positioned than others to fulfil this role, espe-

* Cognitive behavioural therapy in ME/CFS; Standpoint of the ME and Disability Support Group. <http://www.steun-groep.nl/cgt/cgtstandpunt.htm> (consulted on 20 December 2004).

cially as the relationship between physician and patient has frequently already been put to the test in the prechronic phase. It is essential to look closely at this situation before continuing to treat the patient. For those CFS patients who have a job, the occupational physician and the insurance physician are also important. Quite a few patients are dissatisfied with the state of affairs in this regard and they complain, in particular, of inequality in treatment. The Committee believes that patients are entitled to a uniform approach and methodology. Guidelines for fatigue symptoms should be capable of satisfying this requirement, providing that the relevant medical disciplines apply the same basic principles. Only then will there be consistency in the approach adopted by the different physicians encountered by the patient.

The Committee urges the relevant professional organisations* to formulate guidelines for the management of fatigue symptoms that are based on a common set of fundamental principles and cooperation agreements.

6.6.2 *Patients who do not benefit from, are not eligible for, or do not wish to undergo CBT*

There are patients who do not benefit from CBT or who prematurely drop out. CBT is not an option for every patient. Some patients do not wish to undergo this form of therapy, patients who are involved in procedures relating to social security benefit are (temporarily) ineligible (6.5.3), and CFS patients with extremely severe symptoms are not capable of following an outpatient programme. 'Het Roessingh' Rehabilitation Centre, in cooperation with the NKCv, has introduced a scheme whereby patients can be admitted and then given a course of CBT. This form of treatment is also available at Hoensbroek Rehabilitation Centre (albeit only on a research basis for the time being). For the remaining patients who do not benefit from CBT, and for those who are not eligible for (or do not wish to undergo) this form of therapy, it is still important to show understanding, to stress the possibility of spontaneous recovery**, to control symptoms and to provide rules of behaviour, with the emphasis on building up (physical) activities, including a return to work.

6.6.3 *Treatment capacity*

In practice, there is currently limited scope for providing CBT to CFS patients. Outpatient treatment is only available on a formal basis at the NKCv. Patient demand exceeds the available resources, and there are consequently 300 to 350 patients now on the wait-

* Netherlands Society of General Medical Practitioners (NHG), Dutch Institute for Healthcare (CBO), Dutch Association for Medical Services in Industry (NVvAB), Dutch Association for Insurance Medicine (NvVG)

** See the Dutch CFS/ME Association's publication MEdium: 'Hurray, an improvement at last. Readers report on their experiences' (in Dutch). Volume 17, No. 2, June 2004.

ing list. The NKCv is investigating how CBT might be made available on a larger scale. Mental health care facilities have been chosen as places where the therapy can be practised. An important reason for this is that only a few primary-care psychologists possess the requisite training and experience in behavioural therapy (nor, in fact, do mental-health psychologists necessarily have sufficient qualifications to carry out this treatment). There is thus an urgent need for more attention to be paid in the training of psychologists to the use of behavioural therapy in treating physical symptoms. This is important not only for the treatment of patients with CFS, but for all patients with unexplained physical symptoms.

One of the options is to create more treatment centres that offer CBT for CFS patients (by analogy with the Nijmegen programme). The NKCv is willing to share its expertise with any new treatment centres. Another option is to create centres for the research and treatment of stress-related disorders (CFS, burnout, etc.), for which plans are already in place at some universities. There are, at this point in time, no scientific answers to the question as to which of these options would most benefit CFS patients.

Young people and CFS

What has been said about chronic fatigue in adults also applies to young people. However, CFS in young people requires extra attention since it poses a threat to normal, age-appropriate development (e.g. separation from one's parents and the pursuit of autonomy and identity).

7.1 The context

Youngsters with CFS are frequently no longer able to follow a standard school curriculum, do homework, cycle or walk normal distances, or take part in sports and other social activities. School absenteeism grows to be ever more common, resulting in learning disadvantages. Absenteeism is a conspicuous characteristic of young people with CFS^{52,233}. It is more prevalent than in youngsters with other chronic disorders^{38,115,256,257}.

Parents and other family members must make allowances for the limitations of youngsters with CFS. This can impact on the functioning of the family. In point of fact, the available research fails to answer the question as to whether family dysfunction is a result of the disorder or a causal factor.

7.2 Prevalence of CFS in young people

Data concerning the prevalence of CFS in young people are scarce and not readily comparable on account of variations in methodology, the definitions of CFS and the selected

age range. Although it is an established fact that CFS does occur in young people in the Netherlands (as elsewhere), its scale is not entirely clear.

In two relatively recent foreign studies, the prevalence of CFS or CFS-like conditions was estimated at 190 (95% confidence interval: 60-320) per 100,000 in a cohort aged 5 to 15 years and at 340 (340-800) per 100,000 in a cohort aged 8 to 17 years^{55,154}. Both studies conform to the CDC-94 criteria for CFS and the methodology is fairly similar. It is reported in these and other studies that the frequency of the condition increases in direct proportion to age^{55,154,185,256}. CFS is seldom encountered in children under 12 years of age. Findings in the literature regarding the sex distribution of CFS in youngsters are inconclusive^{55,101,154}. No reliable Dutch prevalence figures are available.

7.3 Incidence of CFS in young people

There are no data concerning the incidence of CFS in young people.

7.4 Prognosis

Table 7.1 summarises the outcomes of longitudinal studies conducted among young people with CFS. They are based on data from academic research centres. It appears that the symptoms may well persist for months or even years, but that the outcome is favourable in the majority of the cases^{208,256}.

Table 7.1 Reported global outcomes in young people with CFS. Source: Patel²⁰⁸, adapted.

Reference	Recovered or substantially improved	Unchanged or deteriorated	Duration of the follow-up
Krilov 1998 ¹⁶⁶	40/42 (95%)	2/42 (5%)	1 to 4 years
Feder 1994 ¹⁰³	45/48 (94%)	3/48 (6%)	average 3.8 years
Chalder 2002 ⁵⁶	15/18 (83%)	3/18 (17%)	average 6 months
Bell 2001 ²⁸	28/35 (80%)	7/35 (20%)	average 13 years
Carter 1995 ⁵¹	24/31 (77%)	2/31 (7%)	median 16.9 months
Marshall 1991 ¹⁸⁶	13/17 (77%)	2/17 (12%)	median 26 months
Garralda 1999 ¹¹⁴	17/25 (68%)	8/25 (32%)	average 3.8 years
Gill 2004 ¹¹⁹	9/16 (56%)	7/16 (44%)	average 4.6 years
Smith 1991 ²⁵⁸	8/15 (53%)	7/15 (47%)	average 18.4 months
Stulemeijer 2005 ²⁷⁰	15/34 (44%)	19/34 (56%)	5 months

7.5 Symptoms

The general impression is that the clinical picture in young people (10-18 years) is no different from that in adults^{52,82,233,256,257}. Young people with CFS have more somatic symptoms and more functional limitations than peers with other chronic disorders (such as juvenile arthritis, cancer, cystic fibrosis, migraine or emotional disorders) and more personality problems and psychopathology that cannot entirely be explained as sequela of CFS^{115,223,255,257}.

7.6 The prechronic phase

In young people too, determination of the severity of the functional limitations is also a prerequisite when diagnosing fatigue symptoms²⁵⁵. School absenteeism is an important indicator in this respect. Healthy adolescents are also often tired (and they admit it), but this does not usually cause them to absent themselves from school, whereas absenteeism is the pre-eminent characteristic of young people with CFS. It is also important to ask about the extent of physical and social activities now and in the past, as well as the structure of an average day (including times of getting up and going to bed). There may be subjectively perceived fatigue without this necessarily leading to appreciable limitations in daily life.

As is the case with adults, history-taking (including a developmental and biographical history) is important in order to rule out somatic and psychiatric disorders. It must be borne in mind that puberty can be accompanied by marked physical and behavioural changes and that patients or their parents may erroneously interpret these changes as signs of illness. Diagnostic uncertainty, combined with concern on the part of the parents, can easily lead to excessive laboratory testing and unnecessary specialist referrals, whereas these seldom provide any clues and often merely serve to increase anxiety and uncertainty^{53,83,233,255}.

Because stress, anxiety and depression are not uncommon in young people with CFS, it may be justifiable to consult a psychologist or psychiatrist. As with adults, the reluctance of young people and their parents to accept the possibility of psychological attribution can complicate the search for psychological factors that are associated with the fatigue^{52,255,256}.

The relatively good prognosis for young people (Table 7.1) is an additional reason for exercising great restraint in making the diagnosis of CFS during the prechronic phase²⁵⁵.

Treatment in the prechronic phase consists of controlling symptoms (for example by administering NSAIDs for headache and muscle and joint pain^{175,208,255}) and providing rules of behaviour. The main points are:

- attention to a good diet and adequate fluid intake
- careful attention to sleeping habits. Many adolescents with CFS go to bed late, get up late and nevertheless do not feel fully rested; they then sleep for a long time during the day, which in turn disrupts the circadian rhythm
- discouraging physical inactivity and encouraging the (slow) stepping-up of activity
- underlining the importance of maintaining a normal routine (as far as possible) with regard to school and studying, and social and physical functioning.

7.7 The role of the parents

The fact that children are heavily dependent on their parents when it comes to forming opinions has a bearing on clinical management. First, it is inadvisable to make the diagnosis of CFS before the child reaches the age of 10, since the presentation of symptoms at that age is, to a great extent, dependent on the way in which they are interpreted by the parents.

Furthermore, it is advisable to initiate separate confidential discussions with the youngster and the parents in order to hear both sides of the story^{154,255,256}. Recognising that non-functional attributions by the parents can stand in the way of the youngster's recovery, and discussing this point with the parents, is an important element in patient management¹⁰⁴. Moreover, the separate discussions foster a feeling of autonomy on the part of the youngster²⁰⁸.

7.8 Treatment

Having finally made the diagnosis of CFS, it is extremely important to provide an explanation of the condition and to emphasise the fact that there is a good chance of recovery (Table 7.1). The remarks made about symptom control and rules of behaviour in the prechronic phase also apply as far as treatment is concerned. Furthermore, a course of CBT may be considered.

The first publication from an RCT on CBT in youngsters indicates that positive results can also be achieved in youngsters²⁷⁰. It is important to actively involve the parents in CBT⁸³. The level of parent participation is dependent partly on their attitude to the content and the objective of the therapy, and partly on the youngster's need for parental guidance. This is usually greater in a 12 year-old than in a 16 year-old. A course of CBT is only worthwhile if the patient and his parents are agreed on the objective and the background. When dealing with youngsters, one should always aim to bring about a

return to school and to overcome any social isolation through a gradual resumption of all other normal activities.

7.9 The school

7.9.1 *School absenteeism as a warning signal*

As has already been stated, regular absenteeism from school can be an indication of incipient CFS (7.1). It is important for schools (i.e. student counsellors, nurses) to be aware of this.

The basic Child Health Services (JGZ) package provides for final contact with youngsters when they are 16 years of age. This should afford an opportunity to detect chronic fatigue symptoms and CFS. However, the Committee has been given to believe that this contact usually consists of a written questionnaire and that there is a strong chance of this not actually reaching the absentees.

7.9.2 *Home education*

There is discussion in the literature about the issue of home education⁵². The Committee is against this because it could act as a perpetuating factor that hinders a return to normality²⁰⁸.

Scientific research

Answers have already been given at various points in the preceding chapters to the Minister's question regarding gaps in our knowledge of CFS and promising avenues of research. The Committee outlines the main issues below.

The Committee has made it clear that large gaps exist in our knowledge of CFS. Delineation of the disorder is problematic (Chapter 3) and epidemiological data are inadequate (Chapters 4 and 7).

As far as the aetiology is concerned, there is strong evidence to suggest that CFS is a multifactorial disorder. Contributory factors can be broken down into three types: pre-disposing, precipitating and perpetuating factors (5.4). The relative influence and importance of each of these factors has not been determined.

There are numerous hypotheses with regard to the pathophysiology of CFS, which usually focus on one particular aspect of the condition and not on the entire spectrum of signs and symptoms. This approach has not yet proved particularly productive. The Committee discusses a pathophysiological model in which CFS is regarded as a stress-related pain and exhaustion syndrome (5.5). It believes that this provides a sound basis for further scientific exploration.

There is little that can be said with any certainty about the prevention of CFS. Although it is likely that the right balance between rest and activity reduces the risk of CFS, there is no hard evidence to support this theory.

As far as the treatment of CFS is concerned, there is an effective procedure – cognitive behavioural therapy – that aims to modify dysfunctional thinking and to build up

physical activity (6.5). Not all patients benefit from this approach. It is possible that other aetiological factors may open up fresh avenues for the development of new interventions, but this possibility remains as yet virtually unexplored.

All of these unresolved questions call for new scientific research. The Committee has revealed something of the nature and the complexity of the condition. It has underlined the fact that the search for a single, specific cause of CFS has proved fruitless and probably will not lead to an explanation of the range of signs and symptoms. If we are to succeed in actually expanding our understanding of the causes and the treatment of CFS, then a multidisciplinary approach will be required in which the interrelationships between the various factors are studied.

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- A The request for advice
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- B The Committee
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- C Key elements of the ICF
(International Classification of Functioning, Disability and Health)
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- D Glossary

Annexes

The Request for Advice

On 7 June 2002 the Health Council received a letter (reference: POG/ZP 2.294.354) containing the request from the Minister of Health, Welfare and Sport, Dr E. Borst-Eilers, for a review of the current level of knowledge of CFS. The request for advice reads as follows:

Dear Professor Knottnerus,

Chronic fatigue syndrome (CFS) imposes considerable limitations on the occupational, social and personal functioning of the people who suffer from it. The clinical picture is surrounded by ambiguity and uncertainty. Views as to the aetiology and possible causes are many and varied. No conclusive explanation has yet been found for the syndrome. In practice, the condition sometimes goes unrecognised (partly because the principal symptoms – fatigue and general malaise – are not specific to CFS and there is no diagnostic test available for determining whether someone has CFS). Consequently, some patients feel that their symptoms are being ignored, which inevitably causes frustration in the concerned individuals.

Absence from work, and virtual or complete exclusion from employment, are common in these patients. A complaint commonly heard from patients is that they are not eligible for social security benefit under the Disability Insurance Act (WAO) because the cause of their symptoms is said to be unknown, or because the limitations that they are experiencing are not deemed to constitute a disease or infirmity. Patients are reported to experience similar problems in connection with the allocation of other services and facilities (under the Act on Provisions for Handicapped People [WVG] for example, or the Law on the Reintegration of Disabled Persons [REA]) and as far as the assessment of their need for healthcare services is concerned.

This can adversely influence the financial position of the concerned patients.

According to an estimate made by the Free University of Amsterdam's Social Economics Institute in 2000, the social costs of CFS are in the region of Eur 250–600 million per year.

I request that you provide a review of current knowledge on CFS. I request that you give particular consideration to the following topics and questions in your recommendations:

- A description of CFS, including its clinical course. The definition of CFS that is applied in the clinical setting and in scientific research. The delineation of, and the overlap with, other somatic and/or psychological disorders and illnesses.
- An estimate of the incidence and prevalence of CFS, now and in the years to come – if possible, also broken down into relevant groups, such as children, adolescents, men and women, and people of different ethnic origin. Is there evidence to suggest that CFS is more prevalent in particular occupational groups?
- A comparison of the incidence and prevalence in the Netherlands with the neighbouring countries and a possible explanation of any differences.
- Possible causes of CFS and any factors (biological, social, sociological, psychological and societal) that influence the syndrome. What is known about the relationship between work and the development and/or persistence of CFS?
- Risk factors and possible preventive measures. Is it possible to prevent (or exert a positive influence over) the development of CFS by means of behavioural, lifestyle or other measures? Are there any known risk factors for CFS and is early detection of (predisposition to) the condition possible or beneficial?
- Possible therapeutic interventions. To what extent are possible therapeutic interventions applied in the Netherlands? What is known about cooperation between occupational physicians and GPs in relation to these patients?
- Gaps in our knowledge about CFS and promising avenues of research.
- Ways of promoting the dissemination of knowledge about this condition among care providers and ensuring that this knowledge is applied in practice.

For your information, I enclose the *Knelpuntenoverzicht* (Review of Problems), dated April 2002, which was compiled by the *ME-Fonds* (ME Fund) and the CFS patient organisations.

Yours sincerely,

The Minister of Health, Welfare and Sport, Dr E. Borst-Eilers

The letter was accompanied by the following discussion paper, compiled by the *ME-Fonds* in cooperation with the other CFS patient organisations:

Chronic fatigue syndrome/ME Review of Problems April 2002

Introduction

The Ministry of Health, Welfare and Sport has requested four organisations concerned with chronic fatigue syndrome/ME (hereinafter referred to as ME/CFS) to produce a survey of the problems associated with ME/CFS. These four organisations include the Dutch ME Association, the *Steungroep ME en Arbeidsongeschiktheid* (ME and Incapacity for Work Support Group) the *ME-Fonds* and the *Vereniging ME-huis in oprichting* (The ME-Home Foundation).

ME/CFS is a chronic, disabling illness that is accompanied by severe exhaustion and a host of other symptoms. Most patients are no longer able to lead a normal life. Going to school and working are frequently a problem. Besides being a personal tragedy, ME/CFS is also a tragedy for the community. The annual costs to society in 2000 were estimated by the Free University of Amsterdam's Social Economics Institute (research report entitled *Maatschappelijke kosten en ME* [Social Costs and ME]) at between 560 million and 1.34 billion guilders (Eur 254–608 million). The number of patients suffering from the illness in the Netherlands appears to have increased. Research conducted among GPs indicates that 27,000 patients were diagnosed in 2000, compared with 17,000 in 1993. This study found that the diagnosis of ME/CFS is often not made in cases where it is applicable. The ME organisations therefore estimate the number of ME patients in the Netherlands to be 30,000. It not unlikely that this will, within a few years, turn out to an underestimate. CFS stands for chronic fatigue syndrome. This illness was formerly known in the medical world as ME. This name is still used in the World Health Organisation's International Statistical Classification of Diseases (ICD-10) and can likewise be found in the widely-used classification for occupational and insurance physicians in the Netherlands. ME was originally an abbreviation of myalgic encephalomyelitis, which proved to be an unsatisfactory name for the illness. However, the abbreviation 'ME' (without the underlying medical terminology) is the name by which the condition is still most widely known among the general public. This is why we have predominantly used the abbreviation 'ME/CFS' in this document.

The problems experienced by ME patients lie in the medical, social and scientific sphere. They have consequently been divided into the following categories in this document:

- A. Problems relating to healthcare
- B. Problems relating to social position
- C. Problems relating to scientific research

A. Problems relating to healthcare

By contrast with many other people with chronic illnesses, ME patients have to contend with a number of specific problems:

1. Incorrect image among physicians, care-givers, those around them and the public

1. ME/CFS claimed not to exist

The United Nations' World Health Organisation (WHO) has recognised ME as a disease. ME has been included in the chapter on 'Diseases of the nervous system' in the 'International Statistical Classification of Diseases and Related Health Problems' (Tenth Revision, ICD-10, World Health Organisation, Geneva 1992, Volume 1, page 424, G93.3). As a Member State, the Netherlands is bound by this classification. In 1994 the ICD-10 was elevated to 'standard' status in the Netherlands at the recommendation of the National Advisory Council for Public Health (NRV). ME also features in the diagnostic codes for occupational and insurance physicians. ME/CFS is nevertheless still frequently not recognised as an illness in the medical world. To this day, there are medical practitioners who maintain that ME/CFS does not exist, and who refuse to apply the diagnostic criteria and make the diagnosis.

2. No diagnostic test available for ME/CFS

There is no laboratory test with which the diagnosis of ME/CFS can be confirmed. The diagnosis is made by testing whether the patient satisfies the diagnostic criteria and by subsequently ruling out every other disease that might possibly cause the symptoms. Although other diseases are diagnosed in the same manner, this nevertheless frequently gives rise to the misconception among practitioners that it is not possible to objectively make the diagnosis of ME/CFS.

3. ME/CFS is claimed to be caused and/or perpetuated by wrongful thinking and wrongful behaviour

Despite considerable evidence from scientific research to suggest that ME/CFS is associated with physical disorders, the precise cause of the illness remains unknown. In the absence of medical evidence, many physicians have been inclined to reach for psychological explanations rather than admitting that they simply do not know. This is definitely the case with ME/CFS. Psychological research into ME/CFS receives disproportionate attention in the Netherlands. A misconception has consequently come to preponderate among physicians and care-givers that the illness is the result of wrongful thinking and wrongful behaviour on the part of the patient. Psychological therapy is often erroneously regarded not as a way of learning how to better cope with the consequences of the illness, but as a way of curing it. There is insufficient scientific evidence to support this presumption. The patient is thus burdened with the idea that he himself is the cause of his illness and that he is himself to blame if the symptoms do not resolve.

2. Diagnosis

1. Usually made (far) too late

There are internationally established diagnostic criteria for the diagnosis of ME/CFS (see Appendix). These consist, in part, of ruling out other conditions that might account for the symptoms. There is insufficient knowledge of these diagnostic criteria both among GPs and among specialists, and the diagnosis is consequently made late and inaccurately. As a result, patients are left in uncertainty for an unnecessarily long time, they are given the wrong diagnosis, the diagnosis of ME/CFS is made where it is not applicable, or else another diagnosis is erroneously missed. This unnecessarily imposes an additional burden on the patient.

2. General practitioners

Virtually no attention is paid to ME/CFS in the training and continuing education of GPs and what little attention is, in fact, paid has a psychological bias. Moreover, research conducted in 2000 has shown that around 13% of GPs do not make this diagnosis or do not wish to investigate whether the diagnosis is applicable. The same research also reveals that 47% of the GPs did not make the diagnosis of ME/CFS in the case that was presented to them, which – according to the researchers – was definitely ME/CFS. The reasons cited for this include uncertainty, objection to the diagnosis and lack of knowledge.

3. Specialists

There are very few specialists who are able to make a proper diagnosis. Furthermore, there is no specific speciality to which ME patients can be referred. Patients who are referred to a specialist are frequently told: “I have not found anything in my field, so you are healthy”.

4. Insufficient diagnostic investigation

In some cases, the diagnosis of ME/CFS is used as an excuse for not conducting any further investigations. Other possible diagnoses may be missed as a result of this, with all the attendant consequences.

3. Treatment and support

1. Too few expert physicians

There are far too few physicians who are able and willing to treat ME/CFS. This also causes problems for the GP, who has few options for effective patient referral.

2. Too few treatment options

The biggest problem is that there is (still) no treatment that is aimed at tackling the cause of ME/CFS. Furthermore, the possibilities for symptom control remain insufficiently explored and exploited.

3. Imposed treatment

Patients sometimes have treatment imposed on them, which can lead to a serious deterioration in their state

of health. This situation applies at some university centres in the case of the combined use of cognitive behavioural therapy and graded exercise.

4. Cognitive behavioural therapy

There is undoubtedly a need for psychological support, in view of the apparently hopeless situation in which many ME patients find themselves. However, the support options are, for the most part, dominated by a controversial protocol (the Nijmegen CBT Protocol).

5. Rehabilitation is seldom (if ever) available

Rehabilitation should help ME patients to make the best possible use of their limited opportunities. Specific rehabilitation is, however, virtually non-existent. Where such facilities are available (e.g. at 'Het Roessingh' in Enschede), there are very long waiting lists and the capacity is extremely limited.

6. Limited reimbursement of treatment

Some regular treatments that can be effective in particular cases are not reimbursed (limited reimbursement for physiotherapy, no reimbursement for specialist treatment abroad). Many alternative treatments that benefit certain patients are likewise not reimbursed.

7. Home care problematic

Owing to the lack of residential treatment options, patients are currently mainly reliant on their GPs. However, GPs often have little opportunity to make home visits owing to lack of time. Furthermore, if the patient has problems, GPs assume that he is ambulatory and will come to them, whereas this is by no means always possible. Ultimately, patients are regularly left to fend entirely for themselves.

8. Patients poorly handled

Patients are frequently poorly handled by physicians, with their symptoms either not taken seriously or trivialised.

B. Social problems

1. Income and social security benefits

1. Exclusion from social security benefits

ME patients who have been declared unfit for work are still sometimes either excluded from receiving social security benefit under the Disability Insurance Act (WAO), the Invalidity Insurance (Young Disabled Persons) Act (Wajong) or the Invalidity Insurance (Self-employed Persons) Act (WAZ). Recent, as yet unpublished, research indicates that 28% of insurance physicians and 27% of occupational physicians are of the opinion that ME/CFS cannot be regarded as a disease or infirmity (a condition for entitlement to a WAO benefit). Plans are constantly being put forward to bar ME patients from receiving disability benefits on the grounds that the cause of the illness remains unknown or else based on a misrepresentation of its cause and of the possibilities for treatment.

2. Determining limitations

There is no sound and undisputed method available for objectively determining the limitations and the physical capacity of people with ME/CFS. The method that is used in the assessments leads to a great deal of arbitrariness.

3. Other financial problems

For the same reasons that lead to the problems with WAO benefits, ME patients can be faced with the prospect of non-payment of wages during the first year of their illness, dismissal without entitlement to unemployment benefit for refusal to work, refusal to pay out on private disability insurance policies, reduction or withdrawal of social security benefit due to non-fulfilment of the obligation to apply for jobs, and exclusion from entitlement to dependents pension.

2. Work

1. Labour disputes

Non-acceptance of the illness or of the associated limitations by an occupational physician, insurance physician and employer frequently leads to labour disputes and dismissal.

2. Modified work and reintegration extremely difficult

Problems with social security benefit frequently make modified work difficult or impossible. Anyone who is still capable of working will often require a drastic reduction of hours if they are to remain in their job,

something that employers usually find undesirable. Occupational reintegration is frequently impossible because no account is taken of the limitation of physical capacity.

3. Exclusion from services/facilities

People with ME/CFS are sometimes barred from receiving services/facilities under the Law on the (Re)integration of Disabled Persons (REA) because they are not regarded as 'disabled'.

As a result of the problems mentioned above, ME patients who could still be partially capable of working are often remain excluded from employment.

3. Education

ME/CFS is an important cause of prolonged sickness absence among pupils in secondary education. Students with ME/CFS in vocational training and higher education also frequently run into difficulty.

1. Adaptation of teaching impossible in practice

While it is possible, in theory, to adapt teaching to the capabilities and limitations of a student with ME/CFS, this often proves extremely difficult, if not impossible, in practice.

2. Education and support not available

There is no proper education and support available for students with ME/CFS.

3. School attendance officers

Pupils with ME/CFS and their parents sometimes encounter problems with school attendance officers who do not accept absence from school.

The result of all these problems is that children and young people with ME/CFS can fall seriously behind with their education. This is, in part, unnecessary and it is difficult to catch up at a later stage.

4. Services and facilities

1. Arbitrariness and exclusion

As far as services and facilities such as those provided under the Act on Provisions for Handicapped People (WVG), disabled parking facilities and home care are concerned, people with ME/CFS have to contend with the same arbitrariness and exclusion as arise in connection with WAO benefits.

5. Life situation

1. Isolation

People with ME/CFS often suffer from isolation, social exclusion and poverty.

Furthermore, they are continually forced on the defensive because those around them and all sorts of official bodies cast doubt on the severity of their condition.

2. Future prospects

Children and young people with ME/CFS miss out on normal development and have a wholly unclear and uncertain future.

6. Social consequences

1. High costs

Research has shown that ME/CFS currently costs society between €254 million and €608 million per year.

2. Increasing number of patients

Research among GPs has shown that the number of diagnosed ME patients in general practice rose from 17,000 in 1993 to 27,000 in 2000. One of the reasons for this increase may be that the diagnosis is less frequently being missed. A rise in the total number of patients is inevitable, however, since the percentage who recover is low and many new clinical cases are constantly emerging. It is likely that the estimate of 30,000 patients will turn out to be too low within a few years. An estimated 5,000 of these 30,000 people are under 25 years of age.

C. Scientific knowledge and scientific research

1. Methodological problems

1. Patient population

ME/CFS research does not appear to define the patient population in a uniform manner. Moreover, each

study delineates the patient population in a different fashion, making it difficult to draw comparisons between one study and another.

2. Control group

A great deal of the research has been conducted without an adequate control group. The results are consequently difficult to evaluate and verify.

3. Scope and duration

In order to make informed judgements regarding the reasons and risk factors underlying ME/CFS, research with large numbers of patients and controls is required. Furthermore, the research should be conducted over a longer period, given the prolonged nature of the illness. Research of this kind has yet to take place, owing to a lack of funding.

4. Biased research in the Netherlands

The research in the Netherlands is too biased towards the psychological treatment modalities and too little research is conducted into:

- the biochemical aspects of ME/CFS
- the (unknown) cause of ME/CFS
- effective therapies
- demographic and epidemiological aspects, such as the distribution of the condition in the Netherlands, incidence and prevalence, risk factors and the course
- methods for gaining a clear picture of the limitations and physical capacity of ME patients
- the implications of the illness for the patient and those around him.

2. Organisational problems

1. Multidisciplinary

The research conducted to date indicates that the cause of the illness is, in all probability, multifactorial.

This underlines how important it is that research into this disorder should be multidisciplinary in design.

This approach is difficult to achieve in the research arena.

2. Structured scientific approach

There is no specific professional group that is treating ME patients and taking the lead in the research field.

This explains why studies with a structured scientific approach fail to get off the ground and why worldwide research results have not been satisfactorily correlated.

3. Status of the research

Far too little funding has been available in the past to permit research into ME/CFS. This research has consequently not been held in high regard in the Netherlands. Many research plans have foundered due to their high-risk nature, and the lack of coordination and funding.

4. Knowledge exchange

There is no central location in the Netherlands where knowledge is available about research conducted within all branches of medicine at home and abroad into ME/CFS. An overview of ongoing domestic and international studies is also lacking. As a result of this, it is extremely difficult for physicians to gather knowledge on this topic. Knowledge exchange is practically impossible.

Conclusion

Some of the problems that have been discussed above are intrinsic to the illness. These will remain insoluble so long as there is no effective means of treatment and effective prevention remains impossible. This requires targeted research.

Other types of problems can, however, be resolved by means of specific measures. These problems are currently causing unnecessary damage to physical and psychological health, and are imposing an unnecessary burden and expense on society.

The Committee

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Key elements of the ICF

(International Classification of Functioning, Disability and Health)³⁴⁸

The ICF is structured around the following components:

- *body functions*: physiological and psychological characteristics of human functioning
- *body structures*: anatomical parts of the body such as organs, limbs and their components
- *activities*: components of an individual's actions
- *participation*: involvement in a life situation
- *environmental factors*: physical, social and attitudinal environment
- *personal factors*: individual background (e.g. age, sex, ethnicity, etc.)

The following terms play a central role in the evaluation:

- *impairments*: abnormalities in (or loss of) functions or anatomical characteristics
- *activity limitations*: difficulties in the execution of a task or action.
- *participation restrictions*: problems participating in social life, including participation in employment

In order to gain insight into the development of the process over time, it is necessary to obtain data concerning level of functioning in different domains at various points in time and, at the same time, to classify external and personal factors that may influence functioning.

The ICF falls into line with the recent tendency to focus on establishing the level of fitness for work rather than on the level of incapacity for work and to regard reintegration into social life (or employment) as a prerequisite for recovery. Participation in social life can exert a positive influence on activities and can in this way have a positive effect on functioning.

If an individual is to be considered unfit for work, then one should always identify logically consistent manifestations of illness at these three levels. If one of these three elements is missing, or if there is no consistent relationship between them, then there is no incapacity due to illness. After all, it may very well be that the disorders are not accompanied by any limitations in activities at the physical level or that there is no obvious relationship between particular limitations in the performance of activities and the identified disorder. There should be a consistent relationship between the illness, the limitations and the reduced ability to work (participate).

Glossary

1 Abbreviations

<i>CDC</i>	Centers for Disease Control
<i>CFS</i>	Chronic Fatigue Syndrome
<i>CBT</i>	Cognitive Behavioural Therapy
<i>DSM</i>	Diagnostic and Statistical Manual of Mental Disorders
<i>FM</i>	Fibromyalgia
<i>GET</i>	Graded Exercise Training: a form of therapy based on the gradual stepping-up of physical activity
<i>GGZ</i>	Mental Health Care
<i>HPA axis</i>	Hypothalamic-Pituitary-Adrenal axis
<i>IBS</i>	Irritable Bowel Syndrome
<i>ICD</i>	International Statistical Classification of Diseases and Related Health Problems
<i>ICF</i>	Idiopathic Chronic Fatigue
<i>JGZ</i>	Child Health Services
<i>MCS</i>	Multiple Chemical Sensitivity
<i>ME</i>	Myalgic Encephalomyelitis
<i>NKCV</i>	Nijmegen Expertise Centre for Chronic Fatigue
<i>RCT</i>	Randomised Controlled Trial

aetiology

the science and study of the causes of disease

agonist

a substance that has the same effect as another substance

antagonist

a substance that impedes or reduces the action of other substances

attribution

see somatic attribution and psychological attribution

case definition

consensus-based descriptions of disorders

case history

interview between the physician and the patient aimed at gathering information on the medical history, and signs and symptoms of a health condition

cognition

mental activities associated with thinking, learning and memory; used here in the sense of: views, ways of thinking and beliefs

comorbidity

co-existing disorder

cortisol

a stress hormone that is produced in the adrenal cortex

hypervigilance (somatic hypervigilance)

phenomenon whereby harmless physiological signals that one would normally ignore are interpreted as signs of danger that subsequently receive constant attention

idiopathic chronic fatigue

chronic fatigue that resembles CFS, but does not satisfy the criteria stipulated in the case definition

immunological

of or relating to immunology

immunology

study of the body's ability to mount resistance to infectious diseases and foreign substances

incidence

the number of new cases of a disease during a specified period in a specified population

learning history

learning processes that have occurred in a person's youth and subsequent development

longitudinal research

research into what occurs over a (long) period of time

multifactorial

dependent on a number of factors

neurasthenia

a condition characterised by chronic fatigue and accompanying symptoms, first described by Beard in 1869

neuroendocrine

relating to 1) nerve cells that release hormones and the effect of those hormones and 2) the relationships between the central nervous system and the endocrine apparatus (organs that produce hormones)

neurohormonal

see neuroendocrine

pathogenesis

the origination and development of diseases

pathophysiology

the science and study of functional changes seen in organisms or organs due to disease

perpetuating factors

factors that cause symptoms to continue and impede recovery

postviral

occurring after a viral infection

precipitating factors

factors that cause susceptible individuals to develop a disease

predisposing factors

factors that determine the differences in the susceptibility of different individuals

prevalence

the number of cases of a disease existing in a given population at a particular moment in time or within a specific period of time

psychological attribution

attribution of symptoms to psychological causes

sensitisation

a process that results in increased sensitivity to stimuli

sick building syndrome

health problems that are attributed to the building in which one works

sickness behaviour

behaviour that is characterised by a tendency to withdraw from social contacts, listlessness, somnolence, impaired concentration and memory, reduced appetite, mild fever and increased sensitivity to pain

somatic

physical

somatic attribution

attribution of symptoms to physical causes

stressor

factor that causes stress

sympathetic nervous system

part of the nervous system that regulates the functioning of the internal organs

validity

the validity of a test or a research finding is the concordance between what is actually measured and what was supposed to be measured

viral

resembling, relating to, or caused by a virus