

The Clinical Features of Myalgic Encephalomyelitis
Melvin Ramsay, M.D., 1986

The onset of the disease is similar to those described in the various recorded outbreaks. Thus it may be sudden and without apparent cause, as in cases where the first intimation of illness is an alarming attack of acute vertigo, but usually there is a history of infection of the upper respiratory tract or, occasionally, the gastrointestinal tract with nausea and/or vomiting.

Instead of an uneventful recovery the patient is dogged by

Persistent and profound fatigue accompanied by a medley of symptoms such as

Headache

Giddiness

Muscle pain, cramps, or twitchings

Muscle tenderness and weakness

Paraesthesiae (numbness or tingling in the extremities)

Frequency of micturition (urination)

Blurred vision and/or diplopia

Hyperacusis (sensitivity to noise sometimes alternating with deafness or normal hearing)

Tinnitus (constant sound in the ears), and a

General sense of "feeling awful."

Some patients report the occurrence of fainting attacks relieved by a small meal or just eating a biscuit; these attacks were the result of hypoglycaemia ...

All cases run a low-grade pyrexia (fever), seldom exceeding 100°F (c. 38°C) and usually subsiding within a week.

A very thorough examination of the central nervous system should be made and this should be accompanied by a careful estimation of muscle power, especially in the limbs and neck.

A search for enlarged lymph nodes should never be omitted.

If muscle power is found to be satisfactory, a re-examination should be made after exercise; a walk of half a mile is sufficient, as very few ME cases can make more.

Once the syndrome is fully established the patient presents a multiplicity of symptoms which can most conveniently be described in three groups.

1. Muscle phenomena

[Fatiguability]: Muscle fatigability, whereby, even after a minor degree of physical effort, three, four or five days, or longer, elapse before full muscle power is restored and constitutes the sheet anchor of diagnosis. Without it I would be unwilling to diagnose a patient as suffering from ME, but it is most important to stress the fact that cases of ME or mild or even moderate severity may have normal muscle power in a remission. In such cases, tests for muscle power should be repeated after exercise.

[Pain:] In severe cases of ME, muscle spasms and twitchings are a prominent feature and give rise to swollen bands of tissue which are acutely tender. In less severe cases, muscle tenderness may not be so readily elicited but careful palpation of the trapezii and gastrocnemii (the muscle groups most commonly involved) with the tip of the forefinger should enable the examiner to detect minute foci or exquisite tenderness....

[Clumsiness:] In the aftermath of the disease patients frequently fumble with relatively simple manoeuvres such as turning a key in a lock or taking the cork of a bottle.

2. Circulatory impairment. Most cases of ME complain of

Cold extremities and

Hypersensitivity to climactic change ...

Ashen-grey facial pallor, some twenty or thirty minutes before the
Patient complains of feeling ill

3. Cerebral dysfunction

The cardinal features:

Impairment of memory,

Impairment of powers of concentration and

Emotional lability

[Other] common deviations from normal cerebral function:

Failure to recall recent or past events,

Difficulty in completing a line of thought ...

Becoming tongue-tied in the middle of a sentence, and a

Strong inclination to use wrong words, saying "door" when they
mean "table" or "hot" when they mean "cold" ...

Complete inability to comprehend a paragraph even after
re-reading it

Bouts of uncontrollable weeping...

Alterations of sleep rhythm or vivid dreams, or both ...

[Accompanying] features [that] can only be attributed to involvement of the
Autonomic nervous system:

Frequency of micturition (urination)

Hyperacusis (hypersensitivity to noise)

Episodic sweating

Orthostatic tachycardia ...

Variability and fluctuation of both symptoms and physical findings in the course of a day is a constant feature in the clinical picture of myalgic encephalomyelitis.

An alarming tendency to become chronic. [Added in the 2nd edition, 1988]

[A. Melvin Ramsay, M.A., M.D. Myalgic Encephalomyelitis and Postviral Fatigue States: The saga of Royal Free disease (London, 1st ed. 1986, 2nd ed. 1988). Ramsay died in 1990. Thanks to Connie Nelson of the UK for making this available to me.]

Canadian Consensus Document for Diagnosing and Treating M.E./CFS (2003)
Overview; Bruce M. Carruthers, MD and Margorie I. van de Sande, Bed

Short Version Bibliography

Ablashi DV, Eastman HB, Owen CB et al. Frequent HHV-6 antibody and HHV-6 reactivation in multiple sclerosis (MS) and chronic fatigue syndrome (CFS) patients. *Clin Virol* 16(3):179-191, May 1, 2000.

Boda WL, Natelson BH, Sisto SA, Tapp WN. Gait abnormalities in patients with the chronic fatigue syndrome. *J Neurol Sci* 131(2):156-161, Aug. 1995.

Bouholaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally-mediated hypotension and the chronic fatigue syndrome. *Journal of the American Medical Association* 274 (12):961-967 Sept. 27, 1995.

Buchwald D, Cheney PR, Peterson DL, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpes virus type 6 infection. *Ann Intern Med* 116(2):103-113, 1992.

Codero DL, Sisto SA, Tapp WN, et al. Decreased vagal power during treadmill walking in patients with chronic fatigue syndrome. *Clin Auton Res* 6(6):329-333, 1994.

Costa DC, Tannock C, Brostoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. *Q J. Med* 88:767-773, 1995.

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De Meirleir K, Bisbal C, Campine I, et al, a 36 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. *Am J Med* 108 (2):99-105, 2000.

Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. *Ann NY Acad Sci* 840:684-697, May 1, 1998.

Fischer B., Le Bon O, Hoffmann G, et al. Sleep anomalies in the chronic fatigue syndrome. A comorbid study. *Neuropsychobiol* 35(3):115-122, 1997.

Fukuda K, Straus SE, Hickie I et al. Chronic Fatigue Syndrome: a comprehensive approach to its definition and study. *Annals Med* 121:953-959, 1994.

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- Jason LA, Torres-Harding SR, Jurgens A, Helgerson J. Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue syndrome, *JCFS* 12 (1):27-52, 2004.
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- Okada T, Tanaka M, Kuratsune H, et al. Mechanisms underlying fatigue: A voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurol* 4:14, 2004.

Handout 3 – U.S. CDC CFS Website – Bibliography
(As of 11 November 2006)

Research: New Knowledge and Publications:

<http://www.cdc.gov/cfs/cfsresearch.htm>

"Listed below are a variety of publications addressing the research, definition, and treatment of Chronic Fatigue Syndrome (CFS)."

1. Publications: New

"New publications on Chronic Fatigue Syndrome (CFS)."

Jones JF, Reeves WC. GBV-C -w a virus without a disease: we cannot give it chronic fatigue syndrome
BMC Infectious Diseases 5:78, 2005.

Jones JF, Nicholson A, Nisenbaum R, Papanicolaou DA, Solomon L, Boneva R, Heim C, Reeves WC
Orthostatic instability in a population-based study of chronic fatigue syndrome
American Journal of Medicine 118:1415.e19-1415.e28, 2005.

Capuron L, Welberg L, Heim C, Wagner D, Solomon L, Papanicolaou DA, Craddock RC, Miller AH, Reeves WC
Neuropsychopharmacology Online publication: 10 November 2005 at
<http://www.acnp.org/citations/Npp111005050502/default.pdf>

L Capuron, G Pagnoni, M Demetrashvili, BJ Woolwine, CB Nemeroff, GS Berns, and AH Miller. Anterior Cingulate Activation and Error Processing During Interferon-Alpha Treatment. Dept of Psych and Behavioral Sciences, Emory University Sch of Med, Atlanta, Georgia. *Biol Psychiatry*. 2005 August 1; 58(3): 190-196.

Reeves WC, Wagner D, Nisenbaum R, Jones JF, Gurbaxani B, Solomon L, Papanicolaou DA, Unger ER, Vernon SD, Heim C; Chronic fatigue syndrome - a clinically empirical approach to its definition and study
BMC Medicine 3:19, 2005

2. Economic Impact

http://www.cdc.gov/cfs/publications/economic_impact.htm

Reynolds KJ, Vernon SD, Bouchery E, Reeves WC. The economic impact of chronic fatigue syndrome.
Cost Effectiveness and Resource Allocation 2:4, 2004.

3. Case Definition

http://www.cdc.gov/cfs/publications/case_definition.htm

"This section contains reviews and abstracts of articles covering the chronic fatigue syndrome (CFS) case definition."

Reeves WC, Wagner D, Nisenbaum R, Jones JF, Gurbaxani B, Solomon L, Papanicolaou DA, Unger ER, Vernon SD, Heim C; Chronic fatigue syndrome - a clinically empirical approach to its definition and study
BMC Medicine 3:19, 2005 [repeat citation]

Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC
Psychometric properties of the CDC symptom inventory for the assessment of chronic fatigue syndrome
Population Health Metrics 2005:3:8.

J Nisenbaum R, Ismail K, Wessley S, Unwin C, Hull L, Reeves WC
Dichotomous factor analysis of symptoms reported by UK and US veterans of the 1991 Gulf War
Population Health Metric 2004; 2:8, 2004

Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, Evengard B, White PD, Nisenbaum R, Unger ER, and the International Chronic Fatigue Syndrome Study Group.
Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution.
BMC Health Services Research 2003;3:25

**** Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, and the International CFS Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine*, Vol. 121:pages 953-959, 1994.**

This is the most current chronic fatigue syndrome (CFS) research case definition that has been published in the peer reviewed literature. A decision was made to revise the 1988 case definition of CFS because it failed to distinguish cases of CFS from other forms of chronic fatigue. The complexities of the condition and its inherent similarity to other forms of prolonged fatigue made it desirable to devise guidelines that would facilitate comparative studies, i.e. studies aimed at discerning any features of CFS that serve to distinguish it from other forms of chronic fatigue. The authors have attempted to devise a comprehensive, systematic, and integrated approach to the evaluation, classification, and study of persons with CFS and other fatiguing illnesses. The article proposes a conceptual framework and a set of guidelines for conducting CFS studies. Included among the guidelines are recommendations for the clinical evaluation of fatigued persons, and a strategy for subgrouping fatigued persons for scientific investigations.

Note: The above paragraph is all that is included; neither article nor definition are included or even linked.

Nisenbaum R, Reyes, M, Mawle AC, Reeves WC. Factor analysis of unexplained severe fatigue and interrelated symptoms: overlap with criteria for chronic fatigue syndrome. *American Journal of Epidemiology*, vol. 148, pages 72-77, 1998.

Holmes GP. Defining the chronic fatigue syndrome. *Reviews in Infectious Diseases*, vol. 13 (suppl 1),pages S553-S555, 1991.

****Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Strauss SE, Jones JF, Dubois RE, Cunningham-Rundles C, Pahwa S, Tosato G, Zegans LS, Purtilo DT, Brown N, Schooles RT, Brus I. Chronic fatigue syndrome: A working case definition. *Annals of Internal Medicine* 108:387-389, 1988. "Summary: This was the first research case definition for CFS published in the peer reviewed medical literature. It was completely revised in 1994."**

Note: The single sentence above is all that is included about the original Holmes 1988 definition. No article, no abstract, no case definition; no link to the case definition.

Fukuda K. Development of the 1994 chronic fatigue syndrome case definition and clinical evaluation guidelines. In: *Chronic Fatigue Syndrome*, edited by Yehuda and Mostofskym. Plenum Press, New York, 1997. Pages 29-94.

"Summary: This is a review chapter which discusses development of the 1994 CFS research case definition and guidelines for clinical evaluation of patients."

Note: The single sentence above is all that is included about that chapter.

Nisenbaum R, Reyes M, Unger ER, Reeves WC. Factor analysis of symptoms among subjects with unexplained chronic fatigue: what can we learn about chronic fatigue syndrome? *Journal of Psychosomatic Research* 56:171-178, 2004.

4. Studies of Causes

"This section contains reviews and abstracts of studies that cover the causes of chronic fatigue syndrome (CFS)."

Jones JF, Reeves WC. GBV-C -w a virus without a disease: we cannot give it chronic fatigue syndrome *BMC Infectious Diseases* 5:78, 2005. [repeat citation]

Jones JF, Nicholson A, Nisenbaum R, Papanicolaou DA, Solomon L, Boneva R, Heim C, Reeves WC Orthostatic Instability in a population-based study of chronic fatigue syndrome [repeat citation] *American Journal of Medicine* 118:1415.e19-1415.e28, 2005.

Capuron L, Welberg L, Heim C, Wagner D, Solomon L, Papanicolaou DA, Craddock RC, Miller AH, Reeves WC. Cognitive dysfunction relates to subjective report of mental fatigue in patients with chronic fatigue syndrome. *Neuropsychopharmacology Online* publication: 10 November 2005 at <http://www.acnp.org/citations/Npp111005050502/default.pdf> [repeat citation]

Raison CL, Broadwell SD, Borisov AS, Manatunga AK, Capuron L, Woolwine BJ, Jacobson IM, Nemeroff CB, Miller AH. Depressive symptoms and viral clearance in patients receiving interferon- α and ribavirin for hepatitis C. *Brain, Behavior and Immunity* 2005; 19:23-27. CDC/Emory University

- Gunn WJ, Komaroff AL, Bell DS, Connell DB, Levine SM, Cheney PR. Anterior cingulate activation and The Interferon- α modeling study: Inability of retroviral tests to identify persons with chronic fatigue syndrome, 1992. *Morbidity and Mortality Weekly Report*, vol. 42, pages 183-190, 1993.
- Raison CL, Broadwell SD, Borisov AS, Manatunga AK, Capuron L, Woolwine BJ, Jacobson IM, Nemeroff CB, Miller AH. Depressive symptoms and viral clearance in patients receiving interferon- α and ribavirin for hepatitis C. *Brain, Behavior, and Immunity* 2005;19:23-27. CDC/Emory University.
- Vernon SD, Reeves WC. Evaluation of autoantibodies to common and neuronal cell antigens in chronic fatigue syndrome. *Journal of Autoimmune Diseases* 2005;2:5.
- Raison CL, Borisov AS, Broadwell SD, Capuron L, Woolwine BJ, Jacobson IM, Nemeroff CB, Miller AH. Depression during pegylated IFN-alpha plus ribavirin therapy: prevalence and prediction. *Journal of Clinical Psychiatry* 2005;66:41-48. CDC/Emory University
- Whistler T, Jones JF, Unger ER, Vernon SD. Exercise responsive genes measured in peripheral blood of women with chronic fatigue syndrome and matched control subjects. *BMC Physiology* 2005;5:5
- Heim C, Bierl C, Nisenbaum R, Wagner D, Reeves WC. Regional prevalence of fatiguing illness in the United States before and after the terrorist attacks of September 11, 2001. *Psychosomatic Medicine* 2004;66:672-678.
- Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *American Journal of Psychiatry*. 2003;160:1554-1565. CDC/Emory University.
- Capuron L, Raison CL, Musselman DL, Lawson DH, Nemeroff CB, Miller AH. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *American Journal of Psychiatry* 2003;160:1342-1345. CDC/Emory University.
- Capuron L, Neuraeter G, Musselman DL, Lawson DH, Nemeroff CB, Fuchs D, Miller AH. Interferon-Alpha-Induced Changes in Tryptophan Metabolism: Relationship to Depression and Paroxetine Treatment. *Biological Psychiatry* 2003;54:906-914. CDC/Emory University.
- Vernon SD, Shukla S, Reeves WC. Absence of Mycoplasma species DNA in chronic fatigue syndrome *Journal of Medical Microbiology* 2003; 52:1027-1028
- Sorensen B, Streim JE, Strand M, Make B, Giclas PC, Fleshner M, Jones JF. Complement activation in a model of chronic fatigue syndrome. *Journal of Allergy and Clinical Immunology* 2003; 112:397-403.
- Gerrity TR, Bates J, Bell DS, Chrousos G, Furst G, Hedrick T, Hurwitz B, Kula RW, Levine SM, Moore RC, Schondorf R. Chronic fatigue syndrome: what role does the autonomic nervous system play in the pathophysiology of this complex illness? CDC/CFIDS Association of America Symposium *NeuroImmunoModulation* 10:134-141, 2002.
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- Nisenbaum R, Barrett DH, Reyes M, Reeves WC. Deployment stressors and a chronic multisymptom illness among Gulf War veterans. *J Nerv Ment Dis* 188:259-266, 2000.
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- Mawle AC, Reyes M, Schmid DS. Is Chronic Fatigue Syndrome an infectious disease? *Infectious Agents and Disease*, vol. 2, pages 387-389, 1994. Infectious disease cannot be dismissed.
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5. Publications: Surveillance

"This section contains reviews and abstracts of articles covering the chronic fatigue syndrome (CFS) surveillance studies."

- Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. *Archives of Internal Medicine* 2003;163:1530-1536.
- Steele L, Dobbins JG, Fukuda K, Reyes M, Randall B, Koppelman M, Reeves WC. The epidemiology of chronic fatigue in San Francisco. *Am J Med* 105(3A):83S-90S, 1998.
- Reyes M, Gary HE, Dobbins JG, Randall B, Steele L, Fukuda K, Holmes GP, Connell DG, Mawle AC, Schmid DS, Stewart JA, Schonberger LB, Gunn WJ, Reeves WC. Surveillance for chronic fatigue syndrome - four U.S. cities, September 1989 through August 1993. *Morbidity and Mortality Weekly Report*, CDC Surveillance Summaries, vol. 46, pages , 1997.

- Nicholson AC, Vernon SD. Exploration of neuroendocrine and immune gene expression in peripheral blood mononuclear cells. *Molecular Brain Research* 2004;129:193-197.
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- Yan SD, Vernon SD, Unger ER, Karem KL. A simplified approach for analysis of SELDI-TOF mass spectrometry data. *Applied Genomics and Proteomics* 2003; 2:71-77.
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- Vernon SD, Unger ER, Rajeevan M, Dimulescu IM, Nisenbaum R, Campbell CE. Reproducibility of alternate probe synthesis approached for gene expression profiling with arrays. *J Mol Diag* 2:124-127, 2000.
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- Rajeevan MS, Vernon SD, Taysavang N, Unger ER. Validation of array-based gene expression profiles by real-time (kinetic) RT-PCR. *J Mol Diag* 3:26-31, 2001.
- Vernon SD, Shukla S, Unger ER, Reeves WC. Analysis of 16S rDNA sequences and circulating cell-free DNA concentration from plasma of a chronic fatigue syndrome and non fatigued subjects. *Biomed Central Microbiology* 2:39, 2002.
- Vernon SD, Unger ER, Dimulescu IM, Rajeevan M, Reeves WC. Utility of the blood for gene expression profiling and biomarker discovery in chronic fatigue syndrome. *Disease Markers* 18: 193-199, 2002.
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10. Medical Management

"This section summarizes a publication that offers guidelines for the diagnosis and treatment of chronic fatigue syndrome (CFS) patients.

Bleijenberg G. Chronic fatigue and chronic fatigue syndrome in the general population
BioMed Central Health Quality of Life Outcomes 2003;1:52.

Jones JF, Nisenbaum R, Reeves WC. Medication use by persons with chronic fatigue syndrome: results of a randomized telephone survey in Wichita Kansas. *BioMed Central Health Quality of Life Outcomes* 2003;1:74

Fukuda K, Gantz NM. Management strategies for chronic fatigue syndrome. *Federal Practitioner* 1995;July: 12-27.
