



What causes chronic fatigue syndrome?

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Thus the use of the placebo for “diagnosis” of whether or not pain is real is misguided.

The placebo effect, thought of as the result of the inert pill, can be better understood as an effect of the relationship between doctor and patient.¹² Adding the doctor’s caring to medical care affects the patient’s experience of treatment, reduces pain, and may affect outcome. This survey makes it clear that doctors continue to use placebos, and most think they help. We cannot afford to dispense with any treatment that works, even if we are not certain how it does.

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- 1 Nitzan U, Lichtenberg P. Questionnaire survey on use of placebo. *BMJ* 2004;329:944-6.
- 2 Hardern RD, Leong FT, Page AV, Shepherd M, Teoh RC. How evidence based are therapeutic decisions taken on a medical admissions unit? *Emerg Med J* 2003;20:447-8.

- 3 Kleinman A, Guess H, Wilentz JS. An overview. In: Guess H, Kleinman A, Kusek J, Engle LW, ed. *The science of the placebo*. London: BMJ Books, 2002:1-32.
- 4 Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001;344:1594-602.
- 5 Hrobjartsson A, Gotzsche P. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2004;3:CD003974.
- 6 Spiegel D, Kraemer H, Carlson R. Is the placebo powerless? [letter]. *N Engl J Med* 2001;345:1276.
- 7 Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. Hyattsville, MD: National Center for Health Statistics, 2004. (Advance data from vital and health statistics; No 343.)
- 8 Vozeh S. Is the increasing use of evidence-based pharmacotherapy causing the renaissance of complementary medicine? *Br J Clin Pharmacol* 2003;56:292-6.
- 9 Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. *Neurosci Biobehav Rev* 2002;26:941-62.
- 10 Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. *Biol Psychiatry* 2003;54:269-82.
- 11 Beecher HK. Relationship of significance of wound to pain experiences. *JAMA* 1956;161:1609-13.
- 12 Brody H. The doctor as therapeutic agent: a placebo effect research agenda. In: Harrington A, editor. *The placebo effect: an interdisciplinary exploration*. Cambridge: Harvard University Press, 1997:77-92.

What causes chronic fatigue syndrome?

Infections, physical inactivity, and enhanced interoception may all play a part

Chronic fatigue syndrome, also known as myalgic encephalomyelitis, is an illness of unknown nature and cause, but most medical authorities now accept its existence.¹⁻³ Research about its cause has been hampered by the absence of a biological marker, the heterogeneous nature of the illness, and difficulties in differentiating cause from effect.^{2,3} Yet, some progress has been made, particularly when causes are divided into predisposing, triggering, and maintaining factors.

Women get chronic fatigue syndrome more commonly than men for unknown reasons, although increasing evidence suggests a genetic influence on the illness.^{1,3} Premorbid mood disorders are replicated risk markers for chronic fatigue syndrome;^{1,3} the risks may be inflated by shared symptoms or they may be markers for those patients with comorbid mood disorders.^{1,3-5} Another replicated premorbid risk marker is increased consulting of a doctor for minor illnesses up to 15 years before diagnosis,^{w1 w2} suggesting a general vulnerability for either ill health or seeking health care, the latter possibly being mediated by comorbid anxiety.⁴

Certain infectious illnesses, such as Epstein-Barr virus, Q fever, and viral meningitis, can trigger chronic fatigue syndrome;^{w3-w8} common upper respiratory infections do not.^{w3 w9} Little evidence exists of persistent infection in patients with chronic fatigue syndrome.^{w10} An immune cause has not been established,⁶ although preliminary research suggests that immune responses to exercise in these patients may be abnormal.^{w11} The symptoms of chronic fatigue syndrome are similar to the symptoms and consequent behaviour of people with acute infection.^{2 w12} A low cortisol level has repeatedly been found to be associated with chronic fatigue syndrome, and recent research suggests this may be secondary to the physical inactivity and sleep disturbance found with long standing chronic fatigue


syndrome.^{7 w13} Illness maintaining factors may include illness beliefs that encourage avoidant coping.^{w14 w15}

Viner and Hotopf publish in this issue a 30 year cohort study of 16 567 babies born in 1970 (p 941), in which they report childhood predictions of self reported chronic fatigue syndrome and myalgic encephalomyelitis developing in adulthood.⁸ Their most important findings were that chronic fatigue syndrome was predicted by having a disabling illness in childhood and never or hardly ever doing sport out of school at age 10. Premorbid psychological distress in either the mother or the child did not predict the illness.

Previous healthcare attendance for ill health does seem to predict corroborated chronic fatigue syndrome.^{w1 w2} Physical ill health in childhood seems to predispose to medically unexplained ill health in adulthood generally only when the childhood diagnosis is uncertain rather than established.^{w16} Neither the mother’s nor the child’s or adolescent’s psychological distress predicted chronic fatigue syndrome, a finding that contrasts with most studies of both children and adults developing the illness.^{w17 w18} Data from Viner and Hotopf’s study may be more reliable, having been gathered contemporaneously. We need to learn how certain childhood illnesses predispose people to later chronic fatigue syndrome.

The novel finding was that 10 year old children who were reported by their mothers to “never or hardly ever” play sport in their spare time had twice the risk of chronic fatigue syndrome in adulthood. In contrast, school sport had no effect; this might be explained by the compulsory nature of some school sport. Although statistically significant being more sedentary was not a strong risk marker, since 84% of those

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who later developed chronic fatigue syndrome were not sedentary, although relying on self reports of chronic fatigue syndrome might have weakened predictions by including misdiagnoses.

If the finding was not a chance one, could being sedentary itself predispose people to chronic fatigue syndrome, or is being sedentary a marker for something else? We know that ambulant patients with chronic fatigue syndrome are at least as physically deconditioned as sedentary but healthy people, even though studies have excluded the most physically disabled patients because of the difficulty in measuring their fitness.⁹ Lack of fitness and inactivity consistently predicted the later development of chronic fatigue syndrome after infectious mononucleosis,^{5 w19} suggesting that either premorbid or early deconditioning is a risk factor in some patients. Getting fitter is not necessary to feel better after a graded exercise programme,⁹ so is there another explanation?

Patients with chronic fatigue syndrome perceive activity as more of an effort than healthy controls and underestimate their cognitive and physical abilities, while being more aware of their internal physiological state, a phenomenon called interoception.^{1 3 9 10 w2 w15}

^{w20-22} How might this be related to being sedentary or having a disabling illness in childhood? Inactivity increases perception of effort with exercise, through both physiological deconditioning and the related cognitive, emotional, and sleep disturbance from being sedentary.^{11 w23 w24} This may enhance or sensitise interoception, perhaps in a similar way to that hypothesised in the related disorder of fibromyalgia.^{w25} The corollary is that this enhanced bodily awareness or interoception may itself cause sedentary behaviour. When an appropriate trigger supervenes in later life, enhanced interoception may predispose some people to chronic fatigue syndrome.⁵ Trials of prevention are required to test this idea.^{11 w26} Treatments that “reprogramme” inte-

reception and increased activity, such as graded exercise therapy and cognitive behaviour therapy, seem to help most patients.¹²

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- 1 Afari N, Buchwald D. Chronic fatigue syndrome: a review. *Am J Psychiatry* 2003;160:221-36.
- 2 Medical Research Council. MRC chronic fatigue syndrome/ME Research Advisory Group. *Chronic fatigue syndrome/ME research strategy*. 2003. www.mrc.ac.uk/pdf-cfs_me_research_strategy.pdf (accessed 18 Oct 2004).
- 3 Working group convened under the auspices of the Royal Australasian College of Physicians. Chronic fatigue syndrome: clinical practice guidelines—2002. *Med J Australia* 2002;176:s17-55.
- 4 Henningsen P, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. *Psychosom Med* 2003;65:528-33.
- 5 White PD, Thomas JM, Kangro HO, Bruce-Jones WDA, Amess J, Crawford DH, et al. Predictions and associations of fatigue syndromes and mood disorders that occur after infectious mononucleosis. *Lancet* 2001;358:1946-54.
- 6 Lyall M, Peakman M, Wessely S. A systematic review and critical evaluation of the immunology of chronic fatigue syndrome. *J Psychosom Res* 2003;55:79-90.
- 7 Cleare AJ. The HPA axis and the genesis of chronic fatigue syndrome. *Trends Endocrinol Metabol* 2004;15:55-9.
- 8 Viner R, Hotopf M. Childhood predictors of self reported chronic fatigue syndrome/myalgic encephalomyelitis in adults: national birth cohort study. *BMJ* 2004;329:941-3.
- 9 Fulcher KY, White PD. Strength and physiological response to exercise in patients with the chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* 2000;69:302-7.
- 10 Cameron OG, Shannon MT, Wilson BA, Strang CL, Hamilton WD, Abrams J, et al. *Visceral sensory neuroscience: interoception*. Oxford: Oxford University Press, 2001.
- 11 Department of Health. At least five times a week: Evidence of the impact of physical activity and its relationship to health. A report from the Chief Medical Officer. Department of Health, 2004. www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/Is/en?CONTENT_ID=4080994&chk=1FtLOf (accessed 18 Oct 2004).
- 12 Whiting P, Bagnall A, Sowden A, Cornell J, Mulrow C, Ramirez G. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. *JAMA* 2001;286:1360-8.

Reforming the consultant contract again?

Issues related to financial incentives have changed little and need to be addressed

After protracted negotiations, the BMA and the consultant body voted in favour of a new contract, implemented with effect from April 2004. This contract applies to new practitioners and existing consultants who choose it. During negotiations, the Department of Health sought, but failed to obtain, professional support for a system of fee for service payments, for surgeons in particular. Despite this rejection, professional support among surgeons may now be emerging for the introduction of such a system.

The government's NHS Plan requires considerable increases in medical and surgical activity.¹ This can be achieved by changing the size of the medical workforce or by using incentives to stimulate existing doctors to produce more activity. Contracts of NHS hospital consultants include systems of reward and regulation, and both influence activity. Regulation has developed with the evolution of job plans and appraisal, and it will

develop further with revalidation and more performance management by trusts. Reward systems and financial incentives, however, have changed little in the new consultant contract.

The current lack of transparent accountability of consultants is unlikely to be altered by the new contract. This concern, together with fundamental changes in the private healthcare market, may lead to a revision of the consultant contract. Consultants' income from private practice is currently being undermined in terms of volume of private activity and the price paid for it. The government's ambitious access targets, in reducing waiting times, could affect the volume of activity by reducing private purchase of health insurance, the attractiveness of company health insurance, and the number of people who pay out of pocket. Fees derived from private practice, currently higher in Britain than in Germany, the United States, and Australia, are also under threat.² The government