VIEWPOINT

Chronic fatigue syndrome: understanding a complex illness

Stephen T. Holgate, Anthony L. Komaroff, Dennis Mangan and Simon Wessely

Abstract | Chronic fatigue syndrome (CFS) is a debilitating illness that affects many people. It has been marred by controversy, from initial scepticism in the medical community about the existence of the condition itself to continuing disagreements — mainly between some patient advocacy groups on one side, and researchers and physicians on the other — about the name for the illness, its aetiology, its pathophysiology and the effectiveness of the few currently available treatments. The role of the CNS in the disease is central in many of these discussions. *Nature Reviews Neuroscience* asked four scientists involved in CFS research about their views on the condition, its causes and the future of research aimed at improving our understanding of this chronic illness.

Why do we not know what causes CFS and why is the field so polarized?

Stephen Holgate. For years the medical profession did not acknowledge chronic fatigue syndrome (CFS) as a 'real' condition. The situation became confused when the term myalgic encephalopathy (ME) was introduced and linked to CFS, with many preferring ME because it implied (rightly or wrongly) a concept of mechanisms. In 2002, a *Lancet* commentary noted, "The fact that both names for the illness were used symbolizes respect for different viewpoints while acknowledging the continuing lack of consensus on a universally acceptable name." This confusion has been further compounded by major disagreements over the prevalence and pathophysiology of the illness, let alone the extraordinary range of available treatments, only a few of which have any evidence base. As a result, medical practitioners still view the diagnosis of CFS with great uncertainty and sometimes with outright denial. It is this view that creates a particularly polarized debate with — and sometimes an angry response from — patients. The division is especially great between patient groups and healthcare professionals who think that the syndrome has only psychological and psychosocial causes. This division is a main reason for patients receiving poor healthcare and for the erosion of patient–medical practitioner trust.

Anthony L. Komaroff. We do not know the cause of CFS for the same reason that we do not know the cause of many neurologic diseases: we have not yet been clever enough to figure it out. If the word 'polarized' means that opinions will remain unchanged regardless of the evidence, I would like to think that this is not the case. And I am not sure that the CFS field is more polarized than other fields. The reception that the prion hypothesis (which states that a prion is a protein that can replicate without the use of nucleic acid) received for more than a decade comes to mind. So, too, does the current debate over the possible aetiologic role of Epstein–Barr virus in multiple sclerosis.

CFS is controversial because the case definitions (that is, how the illness being studied is defined) of CFS consist exclusively of symptoms — and obviously anyone can say they have the constellation of symptoms that meets the case definition. Sceptics rightly ask whether there is evidence of objective biological abnormalities underlying CFS. In my judgment, the literature demonstrates many such abnormalities, both when patients with CFS are compared to healthy controls and when they are compared to patients with other fatiguing illnesses, such as multiple sclerosis or major depression. Many of the documented abnormalities involve the central and autonomic nervous systems. In my experience, most sceptics are unaware of the extensive literature citing such abnormalities and become less sceptical upon reading it.

Dennis Mangan. Despite many years of research, no specific factor has been consistently associated with CFS, an illness that is sometimes referred to as ME. The diagnosis remains one of exclusion — ruling out all other causes — rather than having a test 'for' ME/CFS. A clear definition of the disease remains elusive. The current definitions consist of a list of symptoms that are often, but not always, present and that occur with varying degrees of severity. The current definitions also include a requirement that the associated fatigue has persisted for 6 months (BOX 1).

Simon Wessely. There are many similar disorders of which we do not know the cause, and given that CFS almost certainly does not have one cause, it makes identifying them even more difficult. But this does not mean that we cannot help sufferers. Why is the field so polarized? I am not sure that it is. True, there are some CFS activists who have extreme views, verging on the intolerant, but frankly I think that they are in the minority. Our CFS service at King's College and the Maudsley Hospital in South London, UK — one of the first ever NHS services dedicated just to CFS — has seen over 3,000 sufferers since its inception, and I have interviewed over 1,000 of them. What we see is not antagonism, abuse or intimidation from these patients. Perplexity yes and confusion sometimes — because CFS is a confusing and sometimes baffling condition. But the patients primarily have a burning desire to

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understand and get better from whatever it is that they suffer from. This paints a different picture to what you might conclude from a brief perusal of the internet, where sometimes the loudest voices seem to be more concerned with attacking anyone who disagrees with them, especially if they are unlucky enough to be working in psychiatry or psychology. Likewise, there is probably a fairly broad consensus among clinicians and academics, with only a very small but vocal minority giving an impression of polarization within the field. Unfortunately, as we know from the measles, mumps and rubella (MMR) vaccination–autism saga, polarization and antipathy always make for better media coverage than consensus and collaboration.

Q Why do studies use different classifications of CFS and how crucial are these differences for research into CFS?

S.H. There are currently five case definitions of CFS/ME; however, the most prominent and widely used of these are the Canadian case definition[1] and the 1994 US Centers for Disease Control and Prevention (CDC) case definition[2]. The selection of these two definitions over the others has never been substantiated and it has been criticized for lack of specificity. Although all definitions attempt to capture critical aspects of the illness and to differentiate the symptom complex from similar symptom clusters that are associated with other diseases, none have produced evidence to demonstrate either their accuracy or precision in defining cases of CFS/ME. The root of the difficulty is that CFS/ME is a syndrome and, as with many medical syndromes, there are multiple causes. To call CFS/ME a single disease greatly underestimates the complexity of the problem. Thus, to look for 'the' cause of CFS/ME is a self-defeating exercise. What is now needed is the application of; first, systems approaches to establish subphenotypes of the syndrome through standardized clinical, laboratory and physiological measurements without constraining the data input with preconceived clustering; second, 'omics' and other platform technologies to identify pathways that associate with particular subphenotypes; and third, pathway analyses to identify key pathopysiological processes and 'nodes' of intersection at which focused therapeutic intervention might be effective.

A.L.K. Most studies have used the 1994 case definition that was created with the leadership of the CDC[2]. Two other case definitions — the Canadian[1] and Oxford[3] case definitions — are also used. I suspect that none of these case definitions is likely to describe a very homogeneous group of patients. However, they are the best definitions that researchers have been able to provide, and having these case definitions surely has advanced CFS research. In my view, it also is important to standardize how each element of the case definition is defined. The CDC has recommended ways of doing this.

D.M. There are at least three published case definitions (the 1988 CDC definition[4], the 1994 CDC definition[2] and the 2003 Canadian Expert Consensus Panel definition[1]) and most investigators base their participant inclusion and exclusion criteria on one or more of these. However, sometimes the criteria are modified to be more restrictive, to concentrate on severe disease, or less restrictive, to include the wide variety of people with this syndrome.

Different classifications reflect the lack of a clear aetiology and the complex nature of the syndrome. Meaningful comparisons across studies are not possible unless the enrolment characteristics of both patients and controls are described. It would be helpful if authors would clearly specify and quantify, as far as possible, the specific criteria that were used to decide which subjects to include or exclude in their studies. The criteria that were used to identify control populations should also be clearly specified.

S.W. Case definitions remain vital for research into CFS. At the moment the definition is still symptom-based and indeed there are a number of definitions. In the UK we sometimes use the Oxford criteria[3] but overall the most accepted and used

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He has authored or co-authored over 600 papers, mainly on unexplained symptoms and syndromes, the boundaries of medicine and psychiatry, clinical epidemiology, and more recently military health. He is the Director of the King's Centre for Military Health Research at King's College London, and the Civilian Consultant Advisor in Psychiatry to the British Army.

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definition, including by our unit, is the 1994 CDC case definition[2], which has been cited 1,700 times, 150 of which were last year. There have been attempts to derive a case definition that is somehow 'neurological' (with the implicit, and sometimes explicit, assumption that other case definitions identify something that is 'psychiatric' — whatever that means, although it is rarely something good), but this has not been possible. Adding more symptoms, such as sensitivity to noise or light, to the current case definition makes the association with recognized psychiatric disorders stronger, not weaker as some mistakenly believe. Unless and until a validated biomarker for CFS is discovered, symptom-based case definitions will continue to be used, and although the CDC definition could be improved, it is unlikely to be superseded in the near future.

Box 1 | 1994 Centers for Disease Control and Prevention case definition for CFS

To be diagnosed with chronic fatigue syndrome, a patient must satisfy two criteria[2]:

- Have self-reported persistent or relapsing fatigue for at least 6 consecutive months or longer; other medical conditions of which manifestation includes fatigue must be excluded by clinical diagnosis.
- Concurrently have four or more of the following symptoms: post-exertional malaise, impaired memory or concentration, unrefreshing sleep, muscle pain, multi-joint pain without redness or swelling, tender cervical or axillary lymph nodes, sore throat, headache.

The symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

Q *How strong is the evidence that viral infections and/or immune dysregulation play a part in the aetiology of CFS?*

S.H. The current understanding of CFS/ME is that the syndrome has an external environmental or microbiological trigger, such as chemical exposure or a virus, but that psychological and social factors are important in perpetuating the illness. Certainly, interventions such as cognitive behavioural therapy and graded exercise have been shown to be helpful in some patients[5], but the issue that concerns most patients is the lack of effort by the research community (scientists and clinicians) in trying to understand the triggering factors and how these then translate into chronic disease and disability. The sudden occurrence of CFS/ME in children and previously fit and able athletes, often following a viral (or viral-like) illness, point to important and as yet unidentified triggers. As with other chronic diseases (for example, asthma, inflammatory bowel disease and multiple sclerosis) the initiating events may be similar to those that exacerbate the disease once established. There is accumulating evidence for a wide variety of abnormalities in patients with CFS/ME, including altered innate and adaptive immunity, disordered pain perception, endocrine abnormalities, sleep disorders and cardiovascular dysfunction. This variety does not point to an individual cause or group of causes. The initial xenotropic murine leukemia virus-related virus (XMRV) findings[6] encouraged those who believed in a single causative organism, but subsequent studies have dispelled the initial claims, much to the disappointment of many patients and, indeed, researchers who initially thought an important aetiological insight had been gained. However, one is left with a strong sense that post-viral events are a common trigger of CFS, but how they lead to chronic persistent disease remains unresolved.

A.L.K. I am a clinician and epidemiologist. The majority of the patients with CFS that I have evaluated state categorically that their severe fatiguing illness began with an infectious-like syndrome, characterized by respiratory and/or gastrointestinal symptoms, myalgias (muscle pains), fever and adenopathy (enlargement of lymph glands). In addition, many clinical and epidemiologic studies have described post-infectious fatigue syndromes that occur in association with a variety of viral and bacterial agents. Most persuasive was a prospective study organized by the CDC and conducted in Australia, which documented chronic post-infectious fatigue syndromes in about 10% of subjects following infection with any one of three different agents. There are also many studies that show a state of chronic immune activation in patients with CFS, as well as selective dysfunction (such as impaired natural killer cell function).

I think that the literature suggests that the following hypothesis is reasonable: CFS can be triggered by a variety of infectious agents, particularly agents that the immune system cannot eradicate and that can infect the CNS. A low-grade immunological war then ensues, in both the CNS and periphery, and many of the symptoms of the illness are caused by the effect of cytokines in the CNS. The cytokines may be made in the CNS or they may penetrate a blood–brain barrier that is made porous by CNS inflammation. This hypothesis is unproven but plausible. However, it may not explain all cases that meet case definitions of CFS.

D.M. There is no solid evidence to date that any viral or bacterial infection is associated with ME/CFS. There are many scientific articles claiming to have demonstrated such an association, but none have withstood subsequent scrutiny by scientists that were unaffiliated with the original research. However, many ME/CFS patients have reported that the onset of their symptoms followed an episode of flu-like illness. This observation has led to the theory that any of a number of acute infections can trigger an as yet unidentified pathological process in some people that becomes ME/CFS. Although the contribution of the immune system cannot be discounted and abnormalities in immune function may be associated with ME/CFS, there is no definitive evidence that immune cell dysregulation plays a causative part in the development of this syndrome.

S.W. The evidence that certain infections have the ability to trigger CFS is overwhelming. For example, there is a greater risk of developing CFS after Epstein–Barr virus than other common infections. We do not know why this is so, but elegant longitudinal studies have provided firm evidence for this link. The same applies to Q fever. Immune dysfunction is likewise known to be associated with CFS — we and others, for example, have shown immune activation in patients with CFS. However, we do not know if this indicates that immune activation may have an aetiological role in the disease or, alternatively, if it is confounded by low cortisol levels or sleep dysfunction, both of which are commonly found in CFS patients and both of which are associated with immune activation. Interventions targeted at infective agents and/or immune activation have so far been ineffective.

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Q *Does CFS have a psychiatric and/or psychological component? Why is there such resistance from patient groups against this idea?*

S.H. Psychiatric manifestations clearly play a part in CFS, as in many chronic disabling disorders, but other, unidentified pathophysiological factors may be more directly involved in the CNS manifestations. A key issue that is strongly contested is whether psychiatric symptoms are primary, secondary or occur in parallel with underlying physiological, immunological or inflammatory causes. Many patients hold the view that the medical profession attributes the entire syndrome to psychiatric or psychological disorders in the absence of other mechanisms. This view has been reinforced by the only proven effective interventions being those based on symptom relief rather than on a specific set of underlying aetiological causes. Some patients with CFS/ME also consider that graded exercise, which clinical trials have shown to be moderately beneficial[5], initially worsens their symptoms. The frustration expressed by patients and their support groups reflects a perceived failure by the medical community to appreciate that CFS/ME is a 'real' disease and not 'all in the mind' (a term patients associate with 'imagined' — that is, not real). Technological developments in neuroscience 'such as functional brain imaging' are providing new ways of studying how the CNS is influenced by systemic disorders and vice versa. With such powerful and innovative tools available to explore disease mechanisms, it would be a missed opportunity and a great disservice to CFS/ME patients if these tools could not be used to enhance understanding of this disease because of the prejudice of relatively few individuals.

A.L.K. Some patients resist the suggestion that they have a psychiatric illness because psychiatric illness remains a stigma for many people (including some health professionals). Indeed, some patients with primary depression may imagine, amplify or even fabricate CFS symptoms in order to seek a diagnosis that is more acceptable to them than depression.

Does CFS have a psychiatric component? Many studies have found higher rates of psychiatric illness — particularly mood and anxiety disorders — in patients with CFS than in the population at large. The psychiatric illness typically develops after the onset of CFS and can compound the suffering and require treatment. There is much less evidence that patients with CFS have higher rates of psychiatric illness in the years before the onset of CFS — in other words, that pre-existing psychopathology leads to CFS. And all of the studies that have found psychiatric illness in some patients with CFS simultaneously find many patients with CFS who have no current or lifetime evidence of psychopathology but have the same spectrum of symptoms. Finally, there are a number of objective abnormalities in patients with CFS that are not found in patients with major depression.

D.M. This remains to be determined. Many, if not all, chronic diseases can have an effect on the patient's mental status. Depression, brain fog and impaired cognition are frequently reported by some ME/CFS patients. Research shows reciprocal effects of the immune and endocrine systems on brain and neuronal activity, and thus offers possible explanations for many symptoms that are associated with ME/CFS. However, labelling this complex disease as only a psychiatric illness fails to account for a possible role, for example, of infection, inflammation, immune dysfunction and endocrine disorders in causing the symptoms of the illness.

S.W. I have learned from bitter experience that it is best to answer this question with another. By psychiatric and psychological do you mean hysterical, non-existent or imaginary? In which case the answer is unequivocally no. At other times I vary my question: do you consider illnesses such as schizophrenia, major depression, Alzheimer's disease or autism to be psychiatric or psychological? If you do, then the answer might be yes. Now, having agreed our terminology, what do we know? First, we know that prospective studies have established that the risk of CFS is increased in people with a history of depression. Second, cross-sectional studies that compared CFS with other medical conditions have shown that the proportion of CFS patients with co-morbid psychiatric disorders is too high to be simply explained as a reaction to having the illness but is compatible with the idea that this co-morbidity might reflect a shared underlying CNS dysfunction. Third, we know that, as with other chronic disabling conditions, addressing the pattern of beliefs, emotions and behaviours that CFS sufferers experience doesn't explain why they got ill in the first place but can play an important part in treatment, as confirmed in the large and elegant PACE trial[5].

Why is there such resistance from some quarters? Some sadly continue to answer my first question above in the affirmative. It remains the case that conditions that are perceived or classified as psychiatric in origin are associated with stigma and are still being labelled as being 'all in the mind', and those who suffer from them are not given the same respect as those with 'physical' illnesses. Unless and until this changes, the controversy will persist.

Q *Is CFS ultimately a disease of the CNS (neurological and/or psychiatric)?*

S.H. The variety of systemic symptoms makes it difficult to believe that the primary dysfunction in patients with CFS lies purely in the CNS. However, well documented disorders of the autonomic nervous system, sleep disorders, defective attention, abnormalities in cognition, information processing and recall, stress and hypothalamus–pituitary axis abnormalities, altered sensory and pain perception, and reduced motor speed in patients with CFS point to major CNS involvement. Even the most frequently reported symptom of fatigue alone or post-exertional fatigue could have both central and peripheral neurological components; so little is known about the pathophysiology of different types of fatigue. The occurrence of psychiatric symptoms may be intrinsic to the underlying disease process, similar to the situation in infectious mononucleosis, viral encephalitis and autoimmune disease. In addition, psychiatric manifestations may occur in response to chronic symptoms and functional disability associated with the disease, as is the case in many chronic degenerative and inflammatory disorders. It is clear that systemic, neurological and psychiatric manifestations are all part of the syndrome complex, are interdependent and vary in intensity both between patients and in a single patient over time.

A.L.K. The literature strongly suggests that the CNS and autonomic nervous system are involved in many patients who meet the case definitions for CFS. However, there is no neurologic test that has the sensitivity and specificity necessary to constitute a diagnostic test for CFS.

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Many published studies have compared patients with CFS to patients with other fatiguing illnesses and to healthy control subjects. The studies have employed MRI, functional MRI, positron emission tomography (PET), magnetic resonance spectroscopy of cerebrospinal fluid, measurements of sympathetic and parasympathetic function, cognitive testing, electroencephalographic measurements, and neuroendocrine measurements. As with virtually every question in medicine, the literature is not unanimous in its judgment. But the preponderance of the published evidence indicates that there is neurological dysfunction in CFS. It is not possible to summarize this large literature here in a few words, and I refer interested readers to review articles on this topic.

D.M. The symptoms described by ME/CFS patients, such as light-headedness, migraines, coldness, orthostatic intolerance, vasovagal syncope, muscle weakness and fatigue, all point to a connection with the CNS. However, ME/CFS is too complex to be considered only a disease of the CNS.

S.W. CFS is an illness, but defining it as a disease can only happen once a clear pathology is established. Having said that, if and when that does happen, I would be surprised if the pathology does not involve some dysfunction within the CNS. We already know that the pattern of fatigue and fatigability are central and not peripheral in origin, because all are agreed that mental fatigue and fatigability (such as difficulties in concentration, attention or short-term memory) are cardinal to the condition and, as was shown over 20 years ago, are not core features of fatigue that is related to, for example, primary myopathies or neuropathies. We also know about the problems with effortful cognition and the experienced sense of the effort that characterize the condition. In addition, subtle but distinct changes in the hypothalamus–pituitary–adrenal axis are the most replicated biological abnormality in CFS patients so far. Lastly, however, the term 'neurological and/or psychiatric' emphasises the inadequacies of our current systems of classification to capture these complex disorders. After all, why are schizophrenia or autism still classified as psychiatric — the answer is nothing to do with the nature or aetiology of the condition but simply because psychiatrists treat them, not neurologists.

Q *What is the best way for the field to make progress? How will the recent negative XMRV findings affect research directions in this field? What could be the role of neuroscience in advancing the field?*

S.H. The first point that needs emphasising is that the CFS/ME syndrome is a cause of chronic illness, disability and loss of work. The great challenge that faces the field is how to engage scientists to undertake research into the condition that will translate into new diagnostic tests and treatments that go beyond controlling symptoms. This presupposes that there are underlying organic biological causes that are amenable to detection and intervention. Small studies have been suggestive of this, but many of these are characterized by poor case–control recruitment strategies, inadequate phenotyping and limitations in methodology, including sample collection and storage; this has contributed to the problem of a low-quality evidence base of CFS/ME. Over a number of years the UK Medical Research Council (MRC) has received few applications for CFS/ME funding and these are mostly restricted to epidemiological studies and clinical trials of symptom treatment. This suggests a lack of research capacity in the field. Importantly, the MRC now has a dedicated budget for research into autonomic dysfunction, cognitive symptoms, fatigue, immune dysregulation, pain and sleep disorders in patients with CFS/ME. The proposal for such an initiative came from the interdisciplinary MRC CFS/ME Research Advisory Group that includes experts from a wide range of disciplines as well as input from the major UK-based CFS/ME patient charities. The remit of this group is to review current research into CFS/ME, identify new opportunities and encourage research towards understanding the basis of the disease. The aim of the initiative is to improve understanding of pathophysiological mechanisms in CFS/ME, which will lead to new diagnostic tests and treatments. Fundamental to the approach is the need for new research perspectives, and these will be generated by attracting experts that are not currently working on CFS/ME into the field. To ensure this, the MRC has stipulated that all grant applications must include at least one researcher from outside of the CFS/ME field. The MRC also welcomes the involvement of research-based medical charities in this initiative to help to promote a more unified approach to this difficult syndrome.

A.L.K. Neuroscience already has advanced our understanding of CFS. The best way for the field to make progress is to pursue the many leads that already exist in the literature. The evidence that CFS may reflect human infection with mouse retroviruses (XMRV and the polytropic murine leukemia viruses (MLVs))[6] has been seriously challenged. However, this does not alter the evidence of neurologic dysfunction in CFS, and it does not have a bearing on evidence linking CFS with other neurotropic viruses — particularly human herpesvirus 6 and enteroviruses. There are many leads for neuroscientists to pursue in uncovering the pathology and the aetiology of this terribly debilitating illness that afflicts nearly 1% of adults.

D.M. Research into the pathogenesis of ME/CFS is essential to obtain a better understanding of this illness and its determinants, and to identify preventive and/or therapeutic targets. The complex symptomatology of ME/CFS can be challenging to study, not in small part because the syndrome is heterogeneous in its manifestations and perhaps in causation as well. A common case definition of ME/CFS is essential if research studies are to compare data and outcomes across multiple studies.

Research case definitions are needed to fully characterize the neural motor, sensory, cognitive, endocrine and immune manifestations of the illness, to establish clear criteria for diagnosis, and to define subcategories within the broader diagnostic category. Animal models of disease would be very helpful to advance an understanding of the basis of this condition.

The XMRV findings[6] have brought much publicity and interest to the field of ME/CFS. This has resulted in increased interest among researchers to propose pilot projects in their own fields to try to understand this challenging medical problem. The negative XMRV findings underscore the need for further research.

Neuroscientists have been, and will continue to be, key leaders in this arena. Strong connections exist between neuroscience and all domains of ME/CFS research, including infection and inflammation, environmental stress, immune dysfunction, sleep, endocrinology, fatigue and pain. New technologies in molecular biology, genomics and bioimaging are providing exciting, non-invasive ways to investigate brain and neural functions *in vivo*.

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To further interdisciplinary research on ME/CFS, the Trans-US National Institutes of Health (Trans-NIH) ME/CFS Research Working Group identifies cross-cutting areas of research and confronts challenges that embrace multiple scientific areas, including the neurosciences. The Working Group uses conferences, funding initiatives, a website and educational outreach activities to advance research on ME/CFS and attract investigators into this complex field. A related goal of the Working Group is to leverage the resources that are available for ME/CFS research, such as equipment, methodology, supplies and collaborative expert networks. By working as a team, the Working Group considers many ways to support ME/CFS projects that may not otherwise be identified. The Working Group encourages investigators to work together to identify an early diagnosis, treatment and prevention for ME/CFS.

S.W. So long as decent clinical and basic scientists continue to engage with the field it will make progress, although sadly that no longer includes myself. I am no longer active in research in this field, as some of the unpleasantness (and worse) that is mentioned above has taken its toll. I still see CFS patients every week, which remains both satisfying and rewarding. But I now devote most of my time to researching military health and trying to improve medical education. Nevertheless, having been 'with' the subject for most of my professional life, I can take a broader perspective.

The current furore over XMRV is nothing new. It now looks as if it will join the list of other dramatic discoveries in CFS that did not stand the test of time and replication. There is nothing wrong in this: although science can occasionally proceed by a giant leap forward — everyone thinks of *Helicobacter pylori* for example, and the XMRV–CFS link, if it had been true, would have been similar — in reality it more often moves in small incremental steps, which is what I suspect will happen with CFS. CFS is a difficult area whose boundaries are indistinct, and that overlaps with many other symptom-defined conditions, such as fibromyalgia or irritable bowel syndrome. Nearly everyone accepts that it is a heterogenous illness; even if at the moment we cannot distinguish clear divisions or subgroups. It is, however, my opinion that new insights into the nature of CFS are most likely to emerge from the neurosciences, by which I mean basic and clinical neurosciences and psychology. Understanding the nature of the sense of the mental and physical effort that these patients experience and the consequences of experiencing this effort will lie at the heart of it.

But, unfortunately, the XMRV story may also have had unintended consequences beyond generating a rush of papers and citations. The ongoing antagonism that has been directed towards so many of the scientists who failed to replicate the original finding[6] and who thus came up with what the extremists see as the 'wrong answer', has alienated yet another group of scientists from getting involved in this area. This can only be of harm to science and to patients.

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1. Carruthers, B. M. *et al.* Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *J. Chronic Fatigue Syndrome* **11**, 7–36 (2003).
2. Fukuda, K. *et al.* The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann. Intern. Med.* **121**, 953–959 (1994).
3. Sharpe, M. *et al.* A report — chronic fatigue syndrome: guidelines for research. *J. R. Soc. Med.* **84**, 118–121 (1991).
4. Holmes GP. *et al.* Chronic fatigue syndrome: a working case definition. *Ann. Intern. Med.* **108**, 387–389 (1988).
5. White, P. D. *et al.* Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* **377**, 823–836 (2011).
6. Lombardi, V. C. *et al.* Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science* **326**, 585–589 (2009).

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Competing interests statement
S.T.H. declares competing financial interests: see web version for details. The remaining authors declare no competing financial interests.

FURTHER INFORMATION
Centers for Disease Control and Prevention CFS homepage: http://www.cdc.gov/cfs/general/case_definition/index.html
UK Medical Research Council CFS/ME funding homepage: http://www.mrc.ac.uk/Fundingopportunities/Calls/MechanismsofCFSME/MRC007715
Trans-NIH ME/CFS Research Working Group: http://orwh.od.nih.gov/CSF%202011/CFS_home.htm
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