By the time NICE, 2007, recommended Graded Exercise Therapy (GET), the immunology of ME/CFS was well established as complex, reproducible, and biologically meaningful. Key features included NK cell dysfunction; abnormal T-cell activation and suppressor function; cytokine dysregulation (IL-1, IL-2, TNF family); evidence of autoantibodies in subgroups; up-regulation and abnormal processing in antiviral intracellular pathways (2-5A/RNase L); and signs of persistent or reactivated viral infection in many patients. Collectively, these findings supported a model of chronic immune activation with selective immune failure and, in some subgroups, autoimmunity - often triggered or perpetuated by viral agents - directly contradicting the psychosomatic explanation being promoted at the time.

In combination, they provided potential objective biomarkers - salivary HHV6, RNase L profiling, NK cell cytotoxic deficits, the pro-inflammatory cytokine milieu, and the elevated NPY levels - that could have been used to stratify patients, define subtypes, and monitor biological response to treatment.

By the end of the first decade of the twenty-first century, the roadmap toward biologically informed research was visible. However, in a period when the UK was promoting its preferred psychosocial model of ME/CFS, what was missing was not evidence but the institutional will to integrate it into diagnostic guidelines and policy documents. Psychosocial theories, promoted by motivated, influential figures, trumped the biomedical evidence.

Consequences of ignoring the immunological evidence

The consequence was not merely academic disagreement. It was the adoption of therapeutic models that failed to align with known immune and neuroimmune dysfunction. When immune activation is amplified by physiological stress, and antiviral defence is impaired, graded exertion is not a neutral intervention. It had been shown to exacerbate the known pathophysiology within as little as eight minutes of exercise (Light and Light, 2009, Klimas, 2010 and White author of the PACE trial, 2004.) Exercise was proven to be a swift, harmful biological stressor if applied to an already

dysregulated system, which would harm patients.

Yet the 2007 NICE guideline, ignoring the evidence, recommended GET and CBT as primary interventions without incorporating this immunological evidence into risk assessment or patient selection. The PACE trial - the PI of which had already produced a study on immunological abnormalities in 2004 that indicated exercise would harm patients – was designed in the same intellectual climate. It enrolled a biologically heterogeneous population and indiscriminately applied behavioural interventions without stratification by immune phenotype or biological severity. No immune endpoints were measured. No attempt was made to identify patients whose cytotoxic impairment or inflammatory amplification might predict harm from exertion.

All ME patients who were prescribed a course of GET were exposed to harmful consequences. Many deteriorated as a result, some to the point of requiring a wheelchair when previously ambulatory or requiring a feeding tube because of often enforced GET. A few continued to deteriorate and eventually died. (See evidence in the 170 Case Histories GET Harm Files.)

The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 1992, Hyde
Immunological changes after both exercise and activity in chronic fatigue syndrome: a pilot study. White PD, KE Nye, AJ Pinching et al. JCFS 2004:12 (2):51-66).
'The State of CFS Research,' by Prof Klimas, 2006, The CFIDS Chronicle.
The Annals of the New York Academy of Sciences published a series of articles in *Contemporary Challenges in Autoimmunity 2009*
Conference reports from 1983 to 2010

Biomarkers were forecast to be available by 2011

Those identified include NK cell cytotoxicity, perforin and granzyme levels, CD2+CD26+ T-cell function, neuropeptide Y (NPY), specific cytokine profiles, Th2-skewed, and autoantibodies against VIP/PACAP that disrupt a central regulatory system that normally coordinates blood flow, metabolism, neuronal protection, and immune balance.

MYALGIC ENCEPHALOMYELITIS (ME)

The Lost Immunological Evidence

Jenny Wilson
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Myalgic Encephalomyelitis (ME/CFS) is a documented serious multisystem neuroimmune-endocrine-cardiovascular disease with autoimmune features. The Quality-of-Life scores are lower than those of all the major chronic diseases with which it has been compared (Hvidberg, 2015). It is also a potentially fatal disorder, especially if medically mismanaged. Its defining symptom is Post-Exertional Malaise (PEM), a delayed exacerbation of the disease's major symptoms following minimal physical or cognitive activity. Failure to recognise its biomedical pathology constitutes a foreseeable risk of patient harm and a potential regulatory breach.

Immunological Evidence Found in Subsets

From the early 1980s, immunologists documented reproducible abnormalities in immune regulation, antiviral defence, and inflammatory signalling. By the mid-1980s, ME/CFS was described in the biomedical literature as a systemic, immune-mediated disease. Yet, just as the evidence was consolidating, political and professional forces moved to marginalise, reinterpret, or dismiss it.

In the early 1980s, Professor Peter Behan laid the groundwork for the immunological research into ME, the first to characterise it as an immune-mediated disease. The immunological research that followed described an immune system that was chronically dysregulated rather than just overactive, while autoimmune features were noted in subsets.

The totality of the evidence illustrated an immune system that was behaving as though it was ineffectively fighting a persistent infection while inappropriately reacting to environmental stressors, medications and foods normally tolerated, foreshadowing the later understanding of Mast Cell Activation Syndrome.

By 2009, Professor Klimas's team reported at least seven promising biomarkers, intended not only for diagnosis but also to stratify disease severity and guide targeted interventions. These findings supported personalised medicine approaches, such as antivirals for patients with viral reactivation or anti-inflammatories for those with Th2-driven immune dysregulation. She claimed at the 2010 Australian Conference that three of the biomarkers, when combined, would serve as not only a diagnostic test by 2011, but would also stratify and guide individual treatment protocols. These biomarker approaches did not translate into clinical guidelines because psychosocial models were preferred by policymakers.

Summary of Main Findings in Subsets

(i) Early signals (1980s): immune activation + immune weakness

Prof. Peter Behan (1983–1988) reported persistent abnormalities in lymphocyte markers and immune regulation. These changes resembled those seen in persistent/post-viral states rather than simple temporary sickness.

Read & Spickett (Lancet, 1988) reported *IgG1 subclass deficiency* in a subset of patients - a specific antibody gap consistent with subtle immunodeficiency in some people with ME.

Dedra Buchwald and others (late 1980s conference) documented high rates of *circulating immune complexes* and reduced *NK cell number/function* (NK dysfunction reported in up to ~70–75% in some series). These early reports framed ME as an immune-related illness.

ii) Cellular immunity - T cells and NK cells (late 1980s → 1990s)

NK (natural killer) cell dysfunction - markedly reduced cytotoxic activity - was one of the most consistently reported findings. NK cells are frontline antiviral cells; their dysfunction fits with viral reactivation theories.

T-cell abnormalities - many groups reported a pattern of *elevated activated T cells* (high proportion 'switched on'), together with *reduced suppressor/cytotoxic* **(CD4/CD8) function** in a substantial subgroup. This combination looks like an immune system that is chronically driven but losing effective antiviral control.

Nancy Klimas and colleagues (early 1990s) also emphasised that lymphocyte activation profiles in many patients looked like *chronic immune activation/exhaustion* while in severe cases, a very high percentage of lymphocytes appear activated at once.

(iii) Cytokine dysregulation and inflammatory mediators that could explain symptoms

Elevated inflammatory signalling molecules were repeatedly reported in subsets: *IL-1*, *IL-2*, *TNF-α*, *soluble IL-2 receptor (sIL-2R)* and others. Some investigators reported *very high IL-1* in subsets of patients while Il-10, the immune's 'braking system', was deficient or missing.

These cytokine abnormalities could both explain systemic symptoms (feverishness, malaise, cognitive effects) and offer a mechanism for neuroendocrine effects (cytokines acting on the hypothalamus and pituitary).

(iv) Antibodies, autoimmunity and B-cell changes

Several teams found autoantibodies (e.g., ANA, thyroid microsomal antibodies) at higher rates than in controls - consistent with immune dysregulation and a possible autoimmune component.

Altered *B-cell subsets* (some increases in autoreactive B-cell types) were described by Klimas and others, again suggesting an autoimmune component in subgroups.

(v) Antiviral intracellular pathways - the 2-5A / RNase L story

Work by Robert Suhadolnik, Paul Cheney, and colleagues identified abnormal activity of the *2′-5′ oligoadenylate synthetase → RNase L* antiviral pathway in many patients.

(a)This pathway is normally turned on by interferons to

degrade viral RNA. In ME, persistent over-activation or, abnormal forms of RNase L were proposed to cause widespread cellular dysfunction: impaired protein synthesis, altered energy metabolism, and disrupted hormone signalling.

(b) Cheney proposed *phases* of RNase L activity (early high activation → later downregulation) that could explain evolving clinical patterns. Even if the precise molecular details remain debated, these findings pointed strongly to a virus/immune interaction.

vi) Evidence for persistent or reactivated viral infections

Multiple investigators reported associations with enteroviruses, herpesviruses (EBV, CMV) and other agents. Some groups (e.g., Mowbray/Behan/Chai) found viral proteins or enteroviral markers in tissues (muscle, gut) in subsets of patients.

This clinical-laboratory picture - viral markers together with NK/T-cell abnormalities and cytokine activation - supported the model that latent or persistent infections are an important trigger/driver in many cases.

(vii) Patterns and subgroups

By the mid-1990s, investigators (e.g., Klimas, De Meirleir) were identifying distinct immune phenotypes or subgroups: for example, one group with strong TNF/IL-1 activation, another with depressed lymphoproliferation and elevated soluble receptors, and another dominated by low NK activity. Recognising subtypes helps explain variability between studies and between patients.

(viii) Clinical implications recognised before 2007

The immune profile provides biologically plausible mechanisms that account for many clinical features: post-exertional worsening, medication sensitivity, endocrine changes (HPA axis suppression from cytokine/IFN effects), and multisystem symptoms. Importantly, the cumulative picture by 2007 was of objective immune abnormalities, challenging claims that ME was a psychosocial disorder as promoted by the Wessely School.