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**Myalgic Encephalomyelitis (ME):
a review with emphasis on key findings in biomedical research.**

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Abstract

This review examines research findings in ME in the light of the current debate about this multiple symptom, multi-organ, multi-system illness and the conflicting views in medicine. These issues cannot be separated from the political opinions and assertions that conflict with the science and medicine and will be part of this review since they have enormous consequences for scientific and medical research, patients, clinicians, carers, and policy makers.

Introduction

Syndromes of uncertain origin reported in the medical literature include myalgic encephalomyelitis-chronic fatigue syndrome, ME-CFS, among several others ¹ (Figure 1). These syndromes give rise to constellations of similar symptoms and affect all the major systems and organs of the body. GWS has been labelled the ME of the military and is a frequent diagnosis in the medical records of veterans of the first Gulf war where it is commonly named as Chronic Fatigue Syndrome (CFS). Despite the acknowledged complaints and disabilities of patients, routine blood tests are surprisingly normal, an indication that these syndromes are outside the experience of many modern clinicians and medical administrators. The number of these overlapping syndromes continues to increase (Table 1), for example, the recent addition of aerotoxic syndrome ².

The inclusion of MS and AIDS/HIV in this group (Table 1) points to a common disturbance of both the immune and nervous systems. An ill-founded alternative approach offers a common psychiatric explanation of these syndromes,³ see below.

The challenge of these syndromes to modern medicine is in accord with the growing understanding of the neuroendocrine-immune (NEI) paradigm, sometimes referred to as the psychoneuroimmune (PNI) paradigm. This has emerged as a result of the identification of complex biological messenger molecules that serve to communicate between these NEI systems (Figure 2).

This understanding, supported by extensive human and animal studies, provides an extensive intellectual foundation for the biological approach to investigating these complex and challenging syndromes of uncertain origin. In contrast, the alternative and controversial claims of some psychiatrists that all these syndromes are expressions of somatisation ³ or covered by the biopsychosocial (BPS) theory lack any sound intellectual basis and spell the failure and possible imminent extinction of modern psychiatry ^{5,6}.

“I see psychiatry under attack from all quarters. Some people see a great future for us. I don't share that view. I believe there is a serious risk that psychiatry as we know it will no longer exist in as little as fifteen years. The reason is simply a lack of anything approximating an adequate intellectual framework for our efforts.”⁵

Nomenclature and Definitions

The term myalgic encephalomyelitis (means muscle pain, *my-algic*, with inflammation of the brain and spinal cord, *encephalo-myel-itis*, brain spinal cord inflammation) was first coined by Ramsay and Richardson and has been included by the World Health Organisation (WHO) in their International Classification of Diseases (ICD), since 1969. The currently version ICD-10 lists ME under G.93.3 - neurological conditions. It cannot be emphasised too strongly that this recognition emerged from meticulous clinical observation and examination ⁷.

The contrasting psychiatric view of ME as mass hysteria originated with the work of Beard and MvEvedy in 1970 who, by their own admission, neither physically examined patients nor took careful clinical histories. Despite reservations at the time of publication this view has continued to grow and claim increasing support without any clinical observations or scientific studies. The outcome is works of fiction rather than medicine resulting in gross abuse/neglect of patients⁷. The introduction of the alternative name CFS emerged from a major conference in the USA in 1988 and has recently been acknowledged to be a major error.

“None of the participants in creating the 1988 CFS case definition and name ever expressed any concern that it might TRIVIALISE the illness. We were insensitive to that possibility and WE WERE WRONG.”⁸

ME is still included under G.93.3 with the only alternative allowed names being CFS and post-viral fatigue syndrome, PVFS.

The introduction of the word fatigue has provided ample scope for dissimulation and even deceit. In the UK, it was only as a result of a challenge launched through a debate in the House of Lords^{9,10} that the Minister for Health, Lord Warner, conceded that mistakes had been made in the official documents circulated to general practitioners and policy makers. These were to be corrected. To my knowledge this has not yet been done. Today many patients with fatigue as a major feature of their illness, for example, cancer, chronic obstructive disease, depression, and many others, are being diagnosed with CFS. This has led to confusion, and left clinicians, patients, and carers without recourse to proper clinical and social support. In the case of children, vicious legal proceedings have involved some parents being accused of Munchausen Syndrome by Proxy (MSBP), with sick children taken into ‘care’ where they have suffered unbelievable cruelty¹⁰⁻¹². A common treatment programme advocated for CFS, whatever its origins, consists of Pacing, CBT (cognitive behavioural therapy) and GET (graded exercise therapy). The Government has spent huge sums of money (£8.2 million) on setting up clinics, manned by a psychiatrist(s) and located in psychiatric hospitals, to which CFS patients are commonly referred. Such an approach has been vehemently opposed by patients and carers. Studies among the 25% Group whose members suffer from severe disabling ME that leaves them housebound or bed-bound found that over 90% of its members were dissatisfied with CBT and GET¹³⁻¹⁵ (Table 2). Other reports have found little or no effect with CBT, while GET is frequently positively harmful (see below).

Despite rejection of these advocated therapies and their demonstrable lack of efficacy their promulgators persist in insisting that they are effective and in addition heap scorn and calumny upon sick patients and talk of patients having “perfectionist personalities, maladaptive beliefs, and laziness”¹⁶. One paper¹⁷ retreating from the total claims made earlier speaks of psychological amplification of biological sensitisation and counsels patients, “do not listen to your own body’s signals, do not trust your feelings, do not trust your thoughts.” Presumably the physician should adopt a similar attitude! How then will it be possible to obtain a thorough history or is this restricted only to the perceptions of the clinician?

In a recent Australian editorial,¹⁸ it was emphatically asserted that “one can safely conclude that from these studies that graded physical exercise should become a cornerstone of the management approach for patients with CFS.” Another paper¹⁹ confidently asserted from a poorly refereed presentation that, “Graded Exercise appears to be an effective treatment for CFS and it operates in part by reducing the degree to which patients focus on their symptoms.”

These claims were rejected and medical and scientific evidence presented that made it clear that “[CFS patients] are not deconditioned. Neither their muscle strength nor their exercise capacity is different fromother sedentary members of the community. We remain unaware of any incontrovertible evidence.....[that] various “exercise training” programs suggested in the previous article improve neither physiological, nor psychological, nor clinical status of people with CFS”²⁰. A common claim that ME/CFS equates to clinical burnout found in athletes is also unsustainable since the changes in cortisol levels in burnout cases are the opposite of those found in ME patients²¹.

The current most widely used definition of CFS is that formulated by the Centres for Disease Control (CDC) in 1994. This definition lacks clarity and mentions few clinical signs. It has been challenged by others who call for sub-types²² to be recognised among ME/CFS patients. One recent clinical study showed marked differences between ME/CFS patients and Gulf War Veterans, GWVs, and organophosphate poisoned farmers who share many common symptoms²³.

The CDC 1994 definition is one of exclusion and delay with a confusing emphasis on fatigue. A group of Canadian clinicians with others from the USA and one from Europe with extensive experience of ME/CFS have combined to write “The Canadian Consensus Document for ME/CFS”, 2003²⁴. This authoritative document emerged from extensive clinical engagement with ME/CFS patients involving thousands of hours of history taking and intensive clinical investigations and was endorsed by the whole group before release. Two senior consultants in the UK have endorsed the Consensus Document and a summary entitled, ‘A Clinical Case Definition and Guidelines for Medical Practitioners’ was circulated with the information for this conference²⁵. It is no longer possible for any UK clinician to assert that there are no valid clinical tests for physicians to use when investigating ME patients. The Consensus Document lists clinical signs that address neurological, immunological, and endocrinological dysfunction and damage in ME/CFS patients that are consistent with the many symptoms described by patients with ME/CFS.

Recent Biomedical Research

Enteroviruses

An important review²⁶, concludes that

“Enteroviruses are well known causes of acute respiratory and gastrointestinal infections, with tropism for the central nervous system, muscle, and heart. Initial reports of chronic enteroviral infections causing debilitating symptoms in patients with CFS were met with skepticism, and largely forgotten for the past decade.....Recent evidence not only confirmed the earlier studies but also clarified the pathological role of viral RNA through antiviral treatment.”

The final bullet points confirm the aetiology, viral persistence, symptom fluctuation, multi-organ damage and possible effective treatment reported in earlier studies^{27,28}.

- A severe flu-like illness occurs in most cases of chronic fatigue syndrome (CFS), suggesting that an infection triggers and possibly perpetuates this syndrome.
- Common viral infections and unusual causes of CFS could be diagnosed based on the details of the initial flu-like illness, if present, epidemiological history, and early virological testing.

- Different laboratories from Europe and recently from the USA have found enteroviral RNA in the tissues, including peripheral blood mononuclear cells and muscles, of patients with CFS.
- Viral persistence through the formation of stable double stranded RNA reconciles the two opposing observations of the past two decades: (1) the absence of live virion in chronically infected patients and animals and (2) the presence of enteroviral RNA in the blood or other tissues.
- Smouldering viral infection of various cells with continuous expression of double stranded RNA and viral antigens could result in a chronic inflammatory state in the local tissues, accounting for the diverse symptoms.
- Interferon- α and interferon- γ act synergistically against enteroviruses *in vitro*, and preliminary studies suggest that this combination may be an effective treatment for patients with chronic enteroviral infection.

In Easter 1990, a major symposium took place in Cambridge, England, and brought together clinicians and scientists who had worked and continue to work on this perplexing illness; together they represent a unique group of experts in this field. Foremost among them was Dr John Richardson. The published proceedings of the conference²⁷, 74 chapters that cover all aspect of ME/CFS, identify it as a multiple symptom, multi-system and multi-organ illness. Many clinical studies and diagnostic procedures are reported (for example, SPECT, PET and MRI scans), and a variety of treatments. John Richardson's major work was published 1 year before he died²⁸. His work emphasises the extensive role of enteroviruses and their effects on the major systems and organs of the body; reports recorded blood flow in the brain with extensive hypofusion in the brainstem and some parts of the cortex that are markedly different from endogenous depression.

Also reported are reduced blood flow through the insula cortex, that controls visceral functions and integrates autonomic information, and in younger ME patients reduced blood flow in the left temporal lobe, that controls access to language²⁹. Magnetic resonance spectroscopy identified increased levels of free choline in the brain which is consistent with a response to an infection resulting in increased breakdown of cell membranes that would result in loss of function³⁰⁻³². This powerful technique should provide a discriminating procedure for diagnosis since in GWVs a different pattern of chemical damage is found.

Richardson also recognised that common symptoms found in ME patients occurred in others exposed to chemical toxins especially organochlorines such as lindane³³. Other scientists have also identified this link. Parkinsonian-like symptoms consistent with damage to the basal ganglia were identified in one young patient²⁸ making a link with the multiple biological and chemical exposures suffered by GWVs. If the knowledge presented in the two major works^{27,28} had been attended to and the bogus psychiatric theories of ME/CFS countered with the careful clinical and scientific studies described in them then much pain and suffering could have been avoided.

Cardiovascular Effects.

A major research group, brought together by John Richardson, continues to investigate questions surrounding ME/CFS and contributors to this informal group have shown how enteroviruses affect the heart^{34,35}. Subsequently Peckerman et al³⁶ described abnormal effects on the heart found in ME/CFS patients that led to the formulation of a useful treatment regimen³⁷.

Extensive damage to the cardiovascular system has been identified by the group at Dundee which demonstrated severe oxidative stress in the endothelium leading to swelling and stiffening³⁸⁻⁴⁰. In one study this high level of oxidative stress distinguished ME/CFS patients from pesticide poisoned farmers and GWVs²³. The identification of this inflammatory condition is consistent with an encephalitis rather than an encephalopathy which is an alternative name being used and canvassed by some ME/CFS groups. Isoprostanes derived from fatty acid metabolism were a key markers used in these studies. Earlier oxidative stress resulting from dysfunctional xenobiotic metabolism was found to be common among ME/CFS patients⁴¹. One marker of this inflammatory condition is high sensitivity C-reactive protein (hsCRP), that correlates with the level of damage in ME patients⁴². Damage to the endothelium in blood vessels supplying the brain, spinal cord and nerves would result in extensive neurological dysfunction. Recently a post-mortem on a person who died from ME found nothing amiss until the spinal cord was examined, when severe inflammation was found¹². Any activities associated with increased free radical production should not be recommended to sick ME/CFS patients as this will intensify the damage. This is why GET is so damaging for many ME patients since exercising muscle is known to generate increased oxidative stress⁴³.

Immunology

Mechanism(s) that underlie the complex immune responses to both viruses, other micro-organisms⁴⁴, and various chemicals⁴⁵ have recently been uncovered with the identification of interferon-induced RNase enzymes. L-RNase has been identified as a dysfunctional form of the enzyme that plays a key role in an aberrant immune response to intracellular micro-organisms. This includes all viruses and microbes that have been implicated in ME, entero- and herpes viruses, parvoviruses, mycoplasmas, chlamydiae, and rickettsiae. *Borrelia* spp. which some feel are major causative organisms in ME are also intracellular organisms that would be expected to provoke the same defensive mechanism. The insights into L-RNase provide a common mechanism for the triggering action of a bewildering variety of micro-organisms and chemicals and suggest possible novel treatments-most notably in the development of amplitgen. Another major feature of ME patients is the low cytotoxicity of circulating NK cells with less effective killing of viruses⁴⁶.

Genetics

The emerging genetic studies on ME/CFS have affirmed and complemented the earlier studies that characterise the complex and far-reaching nature of the illness. An extensive monograph has described the Eta-1/Op paradigm⁴⁷ (early T-cell activation-1 gene and its gene product osteopontin). This gene and its product have a vital role in, initiating the response to infection by viruses (picornaviruses, herpes and HIV), and other microorganisms (including chlamydiae, coxiellae, rickettsiae, and mycobacteria); autoimmune disease; cellular motility and communication; the regulation of phosphate and calcium metabolism and bone growth and development; and numerous other body systems, including bone, joints and tendons, skin, kidney, heart, blood vessels, gastrointestinal system, lungs, central nervous, reproductive, and auditory systems; and neoplasia. The widespread distribution and expression of the Eta-1/Op complex is consistent with the complex and extensive features of ME/CFS and provides a basis for a greater understanding of this illness.

A more recent and comprehensive genetic study⁴⁸ that examined 9,522 genes demonstrated marked changes in the expression of 16 human genes in patients with ME/CFS. Fifteen genes were up-regulated and one down-regulated. These were

associated with, T-cell activation, neuronal function, mitochondria, transcription, translation, the cell cycle, and apoptosis; some of the genes have at present no clearly identified function. An important feature of this study was the use of Taqman technology to carry out real time PCR, polymerase chain reaction, after the preparation of cDNA from the original isolated mRNAs⁴⁹.

Given all the issues around patient selection and the presence of many genes that have yet to be associated with specific functions, this paper is impressive and provides confirmation of the long established, but until recently ignored pioneering work of Ramsay, Richardson, Dowsett and others. An important aspect of this study was the identification of the up-regulated neuropathy target esterase (NTE) gene that plays an important role in neuronal function. NTE affords protection against poisoning by exposure to cholinesterase inhibitors (sarin, organophosphate pesticides and pyridostigmine bromide) that were a feature of the first Gulf War⁵⁰. There can be little doubt now that ME is properly described as an encephalitis associated with up-regulation of pro-inflammatory immune responses with down-regulation of suppressor cytokines. This coupled with the association of this gene with neuronal function validates the WHO nomenclature and classification under neurology and also the name myalgic encephalomyelitis (ME) with the alternative name of post-viral fatigue syndrome (PVFS). It is heartening that the syndromes of uncertain origin (Figure 1) are now seen to have a common basis that provides a much better understanding of these complex illnesses.

Undoubtedly the perverse use of chronic fatigue syndrome, to impose a psychiatric definition for ME/CFS by allying it to fatigue syndromes, has delayed research, the discovery of effective treatment(s), and care and support for those suffering from this illness^{7,11,12}.

I would propose that the use of CFS should now be abandoned and that, following the Minister of Health's assurances, the WHO definition is now accepted and used in all official documentations. The excellent work on the biological aspects of ME, already carried out by several leading research groups, now requires significant funding that will hasten the day when our understanding of these complex syndromes are much better understood.

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Table 1 Symptoms, systems and organs affected by overlapping syndromes of uncertain origin.

SYMPTOMS	OPs	GWS/I	MCS	FMS	CFIDS	MS	HIV/AIDS
JOINT PAIN	+	+	+	around joint area	+	+	+
FATIGUE	+	+	+	+	+	+	+
HEADACHE	+	+	+	+	+	+	+

MEMORY PROBLEMS	+	+	+	+	+	+	+
SLEEP DISTURBED	+	+	+	+	+	?? due to medicines	+
SKIN PROBLEMS	+	+	+	+	+	burning skin	+
CONCENTR^N PROBLEMS	+	+	+	+	+	+	+
DEPRESSION	+	+	+	+	+	+	+
MUSCLE PAIN	+	+	+	+	+	+	+
DIZZINESS	+	+	+	+	+	+	+
G.I. - Irr. Bow.	+	+	+	+	+	+	+
PERIPH PARESTHES/ TINGLING	+	+	+	+	+	+	+
CHEM/ENVIR SENSITIVITY	+	+	+	+	+	Reported	-
EYE PROBLEMS	+	+	+	+	+	+	+
ANXIETY	+	+	+	+	+	+	+
TACHY&/OR CHEST PAIN	+	+	+	+	+	+	+
BREATHING PROBLEMS	+	+	+	Reported	+	+	+
LIGHT SENSITIVITY	+/-	+	+	Reported	+	+	-

Key: + symptom(s) present; - symptom(s) absent. OP = Organophosphate Poisoning; GWS/I = Gulf War Syndrome/Illness; MCS = Multiple Chemical Sensitivity; FMS = Fibromyalgia Syndrome; CFIDS = Chronic Fatigue Immune Dysregulation Syndrome = ME/CFS, myalgic encephalomyelitis/chronic fatigues syndrome; MS = Multiple Sclerosis; HIV/AIDS = Human Immunovirus/Acquired Immune Deficiency Syndrome.

Table 2. 25% Group Questionnaire Responses: Random Sample (437) 66% of Membership. Responses as Percentages of Total Sample

Procedure	Helpful	Unhelpful
Person-centered Counselling	54	46
Psychotherapy	10	90
CBT	7	93

GET	5	95
Pacing	70	30
Alternative Therapies	60	40
Symptomatic Care Management	73	27
Pain Management	75	25

Figure1. Inter-relation of several Syndromes of Uncertain Origin

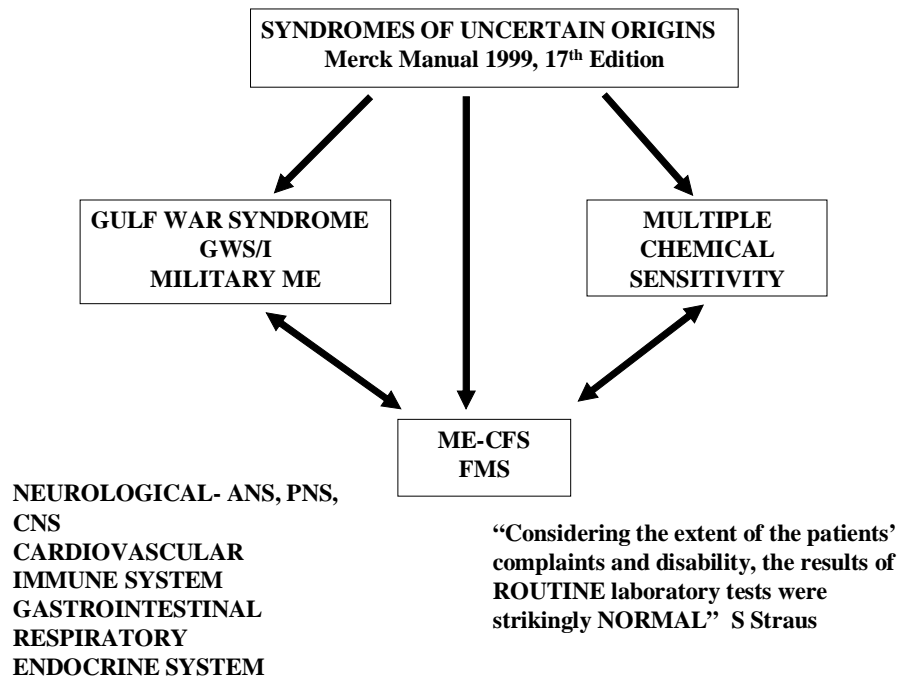
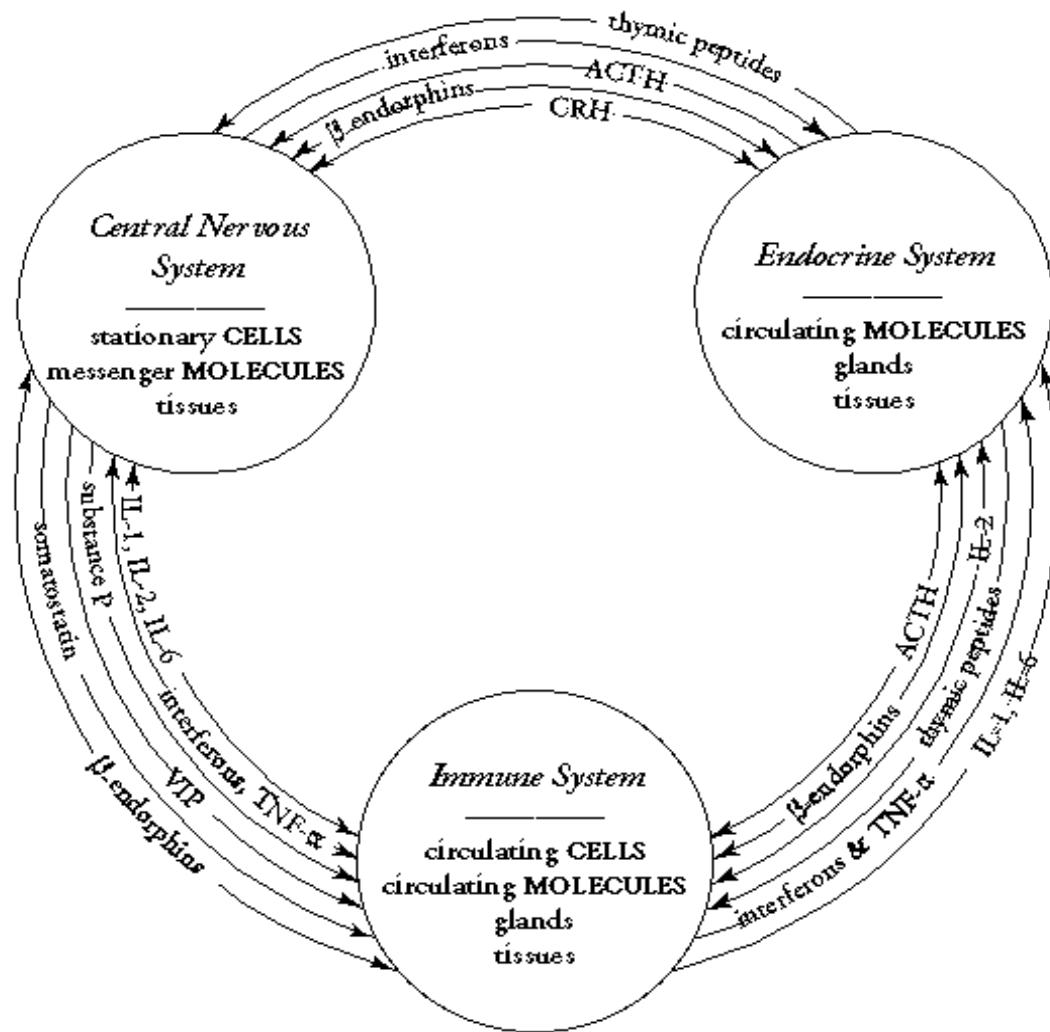


Figure 2. The NEI Comprehensive Integrative Defence System ⁴



Abbreviations: ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; IL, interleukins; TNF, tumor necrosis factor alpha; VIP, vasoactive intestinal peptide.

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