

“Grey” Information about ME/CFS Part 2: 1991 – 1993

Compiled by Margaret Williams 5th May 2011

Part 1 of these extracts from the grey literature on ME/CFS (1956 – 1990) can be seen at: <http://www.meactionuk.org.uk/Grey-Information-on-ME-CFS.htm>

1991: The Spring 1991 issue of The CFIDS Chronicle was a Conference Issue reporting on the CFIDS Association of America Research Conference held on 17th-18th November 1990 at Charlotte, North Carolina. Amongst the notable presentations were the following:

- Marc Iverson, President of the CFIDS Association, said in his Introductory Remarks: *“The impact of this disease can be swift and relentless....I have never known a person with full-blown CFIDS who has not considered suicide at some point or points in his or her illness....**The physical impact is often absolutely devastating. Pain, weakness, exhaustion, dizziness and more than another dozen other symptoms commonly occur....This intellectual impairment is truly bizarre... we have trouble finding words or our way home....Profoundly debilitated, intellectually compromised, unable to emerge from the haze, patients drop from sight....the things that matter to them – relationships, jobs, incomes, homes, families – slip through their fingers**”.*
- Dr Paul Cheney (speaking about The Clinical and Epidemiological Features of CFIDS) said: *“**Early in the course...these patients exhibit disturbances in balance. You can perform simple neurologic tests in the clinic – Romberg and Tandem Stance.** Patients will exhibit difficulties, even athletic individuals, and they’ll be quite surprised at how they can’t seem to stand up... if, in fact, they do not fall over”.*
- Dr Irina Rozovsky (speaking about Levels of Lymphocytes, Soluble Receptors & IL-2 Inhibitors in Sera from CFIDS Patients) said: *“**Chronic fatigue syndrome can be described as an immune dysregulative state, characterised by global immune upregulation with discrete immune defects....Normally T-helper cell activation is mediated by two intracellular signals.**”*

The first signal is the activation of protein kinase C....The second major signal for T-cell activation is the mobilisation of both cytotoxic and extracellular calcium. This activation finally leads to the secretion of interleukin-2 (IL-2) and the expression of IL-2 receptor on the surface of T cells....**Soluble IL-2 receptors have been found in...sera from patients with multiple sclerosis, autoimmune diseases, AIDS, different types of lymphomas and leukaemias and in cancer patients who use IL-2 therapy. It is well-known that patients in IL-2 treatment have the same kind of symptomatology as our chronic fatigue syndrome patients....We have measured the levels of these soluble IL-2 receptors and T8 receptors in chronic fatigue syndrome patients....We have found that our patients have an elevated level of IL-2 receptor compared to healthy controls. Their level of soluble T8 receptor will also be significantly higher than for the control group....These two soluble receptors [IL-2 and T8 receptors], which reflect certain T-cell responses, could be very good markers for the disease and may even reflect the degree of severity of the illness”.**

- Dr John Martin (speaking about Detection of Viral Sequences Using Gene Amplification) said: **“(We have used PCR) in helping to establish that at least a significant number of patients diagnosed as having CFIDS do have a persistent viral infection associated with neurological dysfunction, accompanying metabolic changes, and immunological changes”.**
- Dr Anthony Komaroff said: **“Our model for CFIDS is...that fundamentally, the illness involves a compromised immunity....This compromised immunity leads to a reactivation of latent viruses including HHV-6 and EBV. In some patients, it may well include the enterovirus, coxsackievirus, echo, and even polio viruses....In other patients, environmental toxins could possibly compromise immunity....What all of the data indicates to me is something that will come as no surprise to any of you, and that is that CFIDS is not simply a state of mind”.**
- Dr Daniel Peterson said: **“All of us who treat patients, I think, would agree that **there is a subset of patients with CFIDS who are really very disabled.** Their lives resemble nothing of their former lives; oftentimes they’re bedridden. They interact with nobody....**I have been impressed...by how few patients are malingering, attempting to imitate this disease, or attempting to seek any secondary gains”.****
- Dr Robert Suhadolnik said: **“The 2-5A synthetase/RNase L cell system is a mechanism by which we are able to defend ourselves from viral infections....**We have patients whose RNase L is completely shut down....As we were studying HIV-infected individuals, we found that the HIV retrovirus shuts down the RNase L. Had we not done those studies, we would not have had an explanation for what we’re seeing here.** If there is a retrovirus involved with CFIDS, this would well explain why the system is shut down with respect to the RNase L”.**

- Dr Jack Lieberman (speaking about serum ACE in ME/CFS, which is angiotensin-converting-enzyme, angiotensin being one of the main substances in the body that controls blood pressure) said: *“An elevated serum ACE could very well be a marker for (ME)CFS....(Because high levels of ACE are found in sarcoidosis) a relationship of chronic fatigue syndrome to sarcoidosis must also be considered....**Elevation of serum ACE in patients with CFS lends credence to the concept that CFS is a true disease**”*.
- Dr Denis Wakefield (an immunopathologist from Australia) said: *“I do not think that we should blindly accept the CDC criteria for the diagnosis of this disease....Last year we published, in the Australian Medical Journal, a comprehensive study summarising the immunological abnormalities found in 100 CFS patients compared with age-and sex-matched controls. This group of patients had significant lymphopenia, which occurred in both the helper and suppressor T-cell subsets. They also had increased HLA DR antigen expression on the peripheral blood mononuclear cells....The primary reason your HLA DR antigen rises is because of interferon....**The major conclusion from this study is that the abnormalities that we have observed in the T-cell mediated immunity in people with CFS are not attributable to depression...most of our studies now indicate that the site of pathology in this disease must be within the central nervous system**”*.
- Dr Nancy Klimas said: *“**The most compelling finding was that natural killer cell cytotoxicity in chronic fatigue syndrome was as low as we have ever seen in any disease. This is very, very significant data with very, very low levels of lymphocyte response to mitogens....The actual function was very,very low – 9% cytotoxicity; the mean for the controls was 25. In early HIV and even well into ARC (AIDS-related complex) NK cytotoxicity might be around 13 or 14 percent....Chronic fatigue syndrome patients represent the lowest cytotoxicity of all populations we’ve studied**”*.
- In the moderated Question and Answer session, Dr Klimas warned that in almost every case, any psychiatrically active drug that has been tested has been shown to be immunosuppressive; she specifically warned against the side effects of Prozac (*“Prozac is anything but a benign drug. I would caution anyone who prescribes it to know a lot about the side effects of this drug”*); she warned against the use of the tricyclics in ME/CFS because they suppress immune function and **she pointedly warned against use of lithium (a drug that Simon Wessely recommends for ME/CFS: “There is no doubt that at least half of CFS patients have a disorder of mood. The management of affective disorders is an essential part of the treatment of CFS/ME. Numerous trials attest to the efficacy of tricyclic antidepressants in the treatment of fatigue states. **Patients who fail to respond should be treated along similar lines to those proposed for treatment-resistant depression. Adding a second antidepressant agent, especially lithium, may be beneficial**”) (The chronic fatigue syndrome – myalgic encephalomyelitis or postviral fatigue. S Wessely PK Thomas. In:**

Recent Advances in Clinical Neurology (ed): Christopher Kennard. Churchill Livingstone 1990: pp 85-131).

- Dr Byron Hyde said: ***“Brain mapping has started to change the ideas and the views of physicians across North America. When you show them a photograph of large areas of the brain injured by this disease, they start thinking, maybe I will be next. In Canada, we have a large number of physicians with CFIDS....Look at the primary manifestations of this disease – they reflect central nervous system damage....There are also major, major cardiac aspects of this disease”.***
- Dr Carol Jessop said: ***“I have been involved with CFIDS since 1983....I knew that what (my patients) were telling me was something very serious; it is one of the worst illnesses that I ever heard described to me before....Nausea...seems to increase as the illness goes on....balance problems increase in the chronic stages....98% of patients acutely complained of frequent urination.... Cold extremities are also very common....89% of the patients had irritable bowel syndrome....I am not the only one who has noted the high incidence of endometriosis....87% have fibromyositis. General abdominal tenderness was very common, in 80% of patients....Low magnesium levels are common....Low zinc levels are also common....Both of these trace minerals are absorbed in the gut and, I think, are being malabsorbed by our patients”.***
- Dr Alan Landay said: ***“We have found changes in three markers which seem to be the most significant. First, the CD 11 B marker, which identifies the suppressor cell, decreases in CFIDS patients....There is also an increase in the CD38 and the HLA DR indicating activation....Flow (cytometry) has been a useful tool for studying a number of diseases, including cancer, AIDS, and autoimmune disease. It can identify individuals with immune disorders by using a large panel of markers....Flow cytometry has revealed evidence of CD8 activation in CFIDS”.***
- Dr Jay Levy said: ***“if you look at the activation markers, they are raised in both CFIDS and acute viral illness....Some individuals...will not be able to turn off that activated state. The agent remains as a constant thorn, forcing the immune system to be activated until the agent is eliminated. In these individuals, the immune system never returns to a normal resting state. So these people are in a state of chronic immune activation. What is the result of this chronic immune activation? If an activated white cell is doing its duty, it has to be producing a certain number of lymphokines or cytokines that are working to control the agent that is infecting the body. But these cytokines can have side effects....Cytokines affect the brain, the bowel, the muscle, the liver (which) one sees in CFIDS. So, increased cytokine activation can affect many different tissues in the body (and) can also cause reactivation of other viruses....This disorder could be controlled by eliminating the causative***

*agent or quieting down the hyperimmune system....**There is much clinical information showing that (CFIDS) has often led to other immune diseases....The sequelae...include autoimmune disease and, on some occasions, MS***".

Other speakers discussed functional brain imaging, sleep disorders, abnormal memory processes and speed, distinctive brain patterns seen in ME/CFS and cluster outbreaks of the disease.

1991: In an article entitled "Skeptical of Skeptics", Thomas English, formerly Assistant Clinical Professor of Surgery at Duke University in the US who had to retire due to ME/CFS, wrote: *"Skepticism permeates our profession. It is ingrained during medical training and reinforced by professional experience. To be skeptical is to be detached, rational, and objective. Skepticism is widely perceived as the prudent, conservative way to deal with ambiguous situations....healthy skepticism is the 'in' attitude for intelligent, discriminating physicians. But healthy for whom?....**There is nothing in your experience in medical school, residency, or practice with its gruelling hours and sleep deprivation that even approaches the fatigue you feel with this illness....You, too might wonder about some of your symptoms had you not talked to other patients with similar experiences or talked with physicians who have seen hundreds of similar cases. With experience, a pattern emerges: the bizarre and implausible become commonplace and credible....This is no illness for cookbook doctors. It is a disease for medical intellectuals with supple and open minds**"*(JAMA 1991:265:8:964).

1991: In March 1991 The CFIDS Association produced its first issue of "Physicians' Forum", with contributions from Drs David Bell, Paul Cheney, Jay Goldstein and Charles Lapp. The issue addressed the treatment of CFIDS/ME/CFS and the difficulties this posed because of the complexity and diversity of symptoms; topics covered included nutritional supplements that had been found helpful; intramuscular gamma globulin, anti-inflammatory agents, calcium channel blockers, amplitgen, lifestyle adjustments, stress reduction and symptomatic treatment of specific symptoms. The overriding message came from Dr David Bell: ***"The treatment strategies for CFIDS are still in their infancy, and very little progress will be made until the underlying cause or causes of the illness are clearly defined"***, a view not shared by UK psychiatrists of the Wessely School (see below).

Another view expressed by the US physicians that is not shared by the Wessely School was the emphasis on the need to divide patients into several groups (mild to moderately affected, moderate symptoms but prolonged course, and those with severe symptoms), since the diversity in the clinical picture is the determining factor in symptomatic treatment, yet the Wessely School advocate a "one size fits all" regime of cognitive restructuring (to persuade patients with ME/CFS that they do not have a physical disease) combined with graded aerobic exercise and adjunctive anti-depressants.

1991: On 16th April 1991, Dr Elaine DeFreitas addressed the US House of Representatives Committee on Energy and Subcommittee on Health and the Environment: ***“Let us note at the beginning that CFIDS or CFS/ME is not about being tired. Researchers have demonstrated numerous abnormalities of the immune, muscular, cardiovascular, and central nervous systems in people with CFS/ME; it is truly a multi-system disease with a strong component of immune dysfunction. In fact, one respected scientist called CFS/ME ‘A disease of acquired immunodeficiency’ ”.***

1991: Highlights of the Los Angeles Conference (Chronic Fatigue Syndrome: Current Theory and Treatment; Patient Advocacy Convention) held on 18th-19th May 1991 included presentation of new and important data (reported in The CFIDS Chronicle Fall 1991). Dr Ismael Mena, Director of the Division of Nuclear Medicine at Harbor-UCLA Medical Centre, presented data from SPECT scans of ME/CFS patients. He found ***“significant reduction in blood flow (hypoperfusion) of the temporal lobes amongst CFIDS patients. Seventy percent had hypoperfusion of the temporal lobes, while 45 percent showed reduced blood flow in the frontal lobe. The parietal lobes of 40 percent of CFIDS patients indicated reduced blood flow. These results were obtained from SPECT scans taken while the patients were at rest....Dr Mena conducted a second study to determine if there were any differences in blood flow after exercise....Dr Mena summarised the result of this study by saying: ‘We saw a depression in cerebral blood flow after exercise when we should have observed an increase’. Temporal and frontal lobes seemed to be most affected by exercise. Hypoperfusion after exercise was more pronounced than that exhibited while patients were at rest”.***

Dr James Daly, Co-Director of the Exercise Physiology Laboratory and Director of the Harbor-UCLA Sleep Disorders Laboratory found that most CFIDS (ME/CFS) patients ***“had low normal maximal exercise capacity and oxygen consumption when compared to sedentary controls (the controls were “the most deconditioned people we could find”). In addition: “Several patients with no history of systemic hypertension demonstrated an exaggerated increase in blood pressure during exercise”.*** Daly also found that ***“Many individuals, with no history of lung disease, had low CO2 levels at rest. Low carbon dioxide levels lead to shortness of breath after any amount of exertion and might explain why some people with CFIDS experience bouts of ‘air hunger’ ”.***

1991: In August 1991 the ANZMES (Australia and New Zealand ME Society) magazine “Meeting Place” No: 36 published “Clinical Protocols from America” in which Dr David Bell said: ***“There is a huge spectrum of disease severity in CFIDS (ie. ME/CFS)...Factors which influence the likelihood of spontaneous resolution include the pattern of onset, the severity during the first months or years of illness, the age and sex of the CFIDS patient, and the pattern of the present symptoms (no mention here of maintaining factors being aberrant illness beliefs perpetuating the perceived illness, ie. the Wessely School’s belief)....Patients who have been ill for five years or longer, have prominent neurologic symptoms, and had a gradual onset of symptoms are less likely to experience spontaneous resolution of their symptoms....Unfortunately, there are patients who are very ill with CFIDS, many with very serious neurologic symptoms, where it is unlikely that they will***

spontaneously recover to a normal or near normal level of function....**Very little progress will be made until the underlying cause or causes of the illness are clearly defined**" (this should be compared with Simon Wessely's view that research into aetiology is unnecessary: nine years later he stated: "*Some illnesses are treated without knowledge of the cause....examples include... chronic fatigue syndrome (CFS)*" – New research ideas in Chronic Fatigue. RSM Press; 2000).

In the ANZMES article, Dr Anthony Komaroff from Harvard said: "**Chronic fatigue syndrome represents a state of excessive cytokine production and therefore vitamin utilisation pathways may be partially blocked. For this reason we recommend that multivitamin therapy be employed in the treatment of chronic fatigue syndrome** (sixteen years later NICE, influenced by the Wessely School, effectively prohibited testing for vitamin levels and vitamin/mineral supplementation in ME/CFS patients)*SPECT scanning often reveals larger areas of low blood flow within the temporal lobes*"; Komaroff went on to mention the "**pressure-like headaches and balance disturbances common to this disorder**".

1992: The February 1992 issue of The CFIDS Chronicle carried on its front page a Statement from Dr Walter Gunn, Principal Investigator of CFS studies at the CDC (Centres for Disease Control): "**Our Surveillance Study does not support the notion that CFS is a psychiatric illness, and in fact, suggests that it has an organic basis. Recent published reports suggest that the immune system may be involved in this illness. Additional published research suggests that viruses may also be involved in CFS**".

1992: The September 1992 issue of The CFIDS Association's Physicians' Forum (entitled "CFIDS: The Diagnosis of a Distinct Illness") carried important articles by key players in the ME/CFS stakes, including Drs David Bell, Paul Cheney, Charles Lapp and Nancy Klimas.

Dr Bell stressed the importance of a thorough physical examination and suggested an appropriate laboratory workup for those with suspected ME/CFS; he said: "*Fatigue, sore throat, abdominal pain, headache, lymph node pain, myalgia and arthralgia suggest the presence of viral infection. Neurologic symptoms such as dizziness, balance disorder, parasthesias, and cognitive disturbances involving short-term memory and attention may be present....Neurological abnormalities may include hyper-reflexia in the lower extremities, Romberg's sign and impaired tandem gait....Numerous immunologic abnormalities have been described in patients with chronic fatigue syndrome....Decreased natural killer cell function is perhaps the most reproducible immunologic abnormality....The diagnosis is made on the basis of severe fatigue, a characteristic pattern of symptoms, and exclusion of other illnesses*". The seriousness of the disorder is reflected by the fact that Dr Bell listed the differential diagnoses as including rheumatoid arthritis, lupus erythematosus, Lyme disease, multiple sclerosis, sarcoidosis, hepatitis B, polymyalgia rheumatica, HIV virus infection and malignant disease, whilst Leonard Calabrese categorised the differential diagnoses as endocrinological (hypothyroidism, Addison's disease, diabetes); rheumatological

(fibromyalgia, Sjogren's syndrome, polymyalgia rheumatica, polymyositis); neurological (obstructive sleep syndrome, multiple sclerosis); infectious (Lyme disease, HIV); haematological (anaemia, lymphoma) and renal, hepatic or cardiac disease.

In his presentation entitled "The Diagnosis of Chronic Fatigue Syndrome: An Assertive Approach" that was co-authored by Dr Charles Lapp, Dr Paul Cheney stressed the need for the case for diagnosis by objective criteria. He said: ***"The central problem is case selection. Many patients with CFS are excluded from studies because they seem 'too sick' to have CFS....CFS cases are mixed in with non-cases. Inappropriate controls are sometimes used. Some investigators, aware or unaware of a bias, attract or include in their studies the patients who best fit their view of CFS. This so-called selection bias can markedly affect the observations of a study....The medical evidence cited for CFS asserts that the following are present more or less in every patient during the course of his or her disease: T-cell activation, discrete immune defects, viral activation or re-activation, exercise-related dysfunction, and evidence of brain dysfunction or injury. While none of these tests can stand alone to 'diagnose' the illness, an array of these tests can be used to support this diagnosis"*** (it is worth recalling that in the UK, NICE has effectively proscribed these tests). ***There are a number of criticisms given for using (these) tests in the diagnosis of CFS. They include the following: (1) We lack a gold standard for determining this disorder: if a test abnormality has been shown in the medical literature to be associated with a certain disease, such as a positive ANA in lupus, then it is a valid test to be used in supporting a clinical diagnosis.... (2) Even if there are test abnormalities which can be associated with CFS there is no need to make a more definite diagnosis because there is no treatment for the disease: if this were a valid argument, then it would also apply to multiple sclerosis, many cancers, and even AIDS. Documentation of an illness by objective criteria is important not only to confirm the diagnosis, but also to reassure the patient...Though there may be no scientifically validated treatment options for CFS...there are many therapeutic rationales based on test abnormalities which can defend empiric therapy....In the everyday practice of medicine, empiric therapy is often warranted in severe or functionally devastating illness....(Furthermore), the ability to successfully argue for disability is an extremely important aspect of therapy for this disorder....(3) CFS is a 'self-limited illness': this misperception of CFS is pervasive among many clinicians and the lay public. A debilitating illness lasting years or longer is in fact not self-limited, and it deserves considerable medical attention....Good documentation of this disorder lays the groundwork for future empiric intervention"***.

Cheney then listed 22 physical findings in ME/CFS, stating that ***"Contrary to suggestions by some investigators, abnormalities on physical examination, although sometimes subtle, are usually present"***; he listed 10 routine laboratory tests that are often present in ME/CFS patients; he listed his proposed set of tests for ME/CFS which include 4 tests of immunity and 5 tests of discrete immune defects; 5 tests of viral activation or re-activation; 5 tests of exercise-related dysfunction, and tests of brain dysfunction (structural scans, functional scans and neuropsychometric tests, including the Halstead Reitan battery). Cheney continued: ***"CFS clinical and bench researchers are developing an array of tests which are increasingly sensitive and specific for CFS – particularly when used in combination. When patients present with symptoms that suggest CFS, we believe it is***

in their best interests to ...employ these tests to confirm the diagnosis and to document the nature and extent of each case. This information...enables the patient to make appropriate lifestyle adjustments (including defence of disability claims when necessary)".

Cheney's article was followed by a comprehensive overview as an aid to the diagnosis of ME/CFS by Dr Jay Goldstein, who addressed skin disorders in ME/CFS; headaches; eye problems; ear, nose and throat problems; pulmonary complications ("**Dyspnoea, either at rest or on exertion, is the most frequent [pulmonary] complaint, but is probably centrally mediated**"); cardiac abnormalities ("**coronary artery spasm and microvascular angina should be considered**"); gastrointestinal problems ("**Gastrointestinal complaints are very common, and symptoms of irritable bowel form an integral part of the CFS spectrum of symptoms**" – this should be compared with Professor Peter White's assertion in 2006 that "**bowel symptoms are not part of CFS/ME**"; St Bartholomew's Hospital Chronic Fatigue Services, Stakeholder comments on Chapter 6 of the draft NICE Guideline on "CFS/ME", page 316); pelvic disorders ("**Perhaps the most common pelvic disorder in CFS is endometriosis....Adnexal masses and polycystic ovarian syndrome occur with greater frequency in CFS....A much higher percentage of my patients in a CFS practice have developed ovarian carcinoma that I experienced while practising family medicine**"); genitourinary complaints ("**Dysmenorrhea is also more common in CFS patients, even if endometriosis is not present....The primary genitourinary complaint in the male with CFS involves prostatic discomfort, frequency, and nocturia**"); musculoskeletal abnormalities; neurologic abnormalities ("**fasciculations are fairly common, as are tremors....A Hallpike test is sometimes abnormal in vertiginous patients, as is the Romberg test. Muscle weakness is common....Patients should be followed for the development of multiple sclerosis or, more commonly in my experience, immune polyneuropathy**"); associated carpal tunnel syndrome (CFS) and thoracic outlet syndrome (TOS) ("**carpal tunnel syndrome and thoracic outlet syndrome are fairly common in CFS**"); haematological abnormalities ("**CFS patients often complain of easy bruisability or spontaneous ecchymoses....Platelet function studies are sometime abnormal**"). Goldstein noted that: "**The sed rate is often very low. Immune complexes and positive anti-nuclear antibodies are encountered very frequently....Elevated levels of various cytokines and their receptors are often seen**"; he discussed at length the cytokine abnormalities found in ME/CFS and other distinct laboratory abnormalities, as well as SPECT scan abnormalities, evoked responses testing, PET scan abnormalities, lesions detectable by MRI scans, abnormalities on neuropsychological testing, and functional capacity evaluation (ie. an assessment of the patient's ability to perform work demands and activities of daily living). Goldstein concluded by stating that he knew of no other mechanism than a limbic encephalopathy that could produce the diagnostic constellation seen in ME/CFS, but he pointed out that "**Secondary adrenal insufficiency due to a central mechanism relating to CRH deficiency could be responsible for many CFS symptoms**" (in which he specifically included vertigo, intermittent blurred vision and alopecia).

Dr Nancy Klimas wrote about "Diagnosing CFIDS: An Immunologist's Approach", saying: "**Our group in Miami has been actively working to better understand CFIDS since 1985....Some of this work has helped to develop a sense of diagnostic certainty in the evaluation of CFIDS patients, as well as to identify subgroups that are immunologically different from the majority of CFIDS patients....We**

have found the immune evaluation to be quite important, as it not only helps classify the patient, but often helps to direct the care of the patient". Dr Klimas went on to discuss the level of T-cell activation seen in ME/CFS patients, the diminished cell function, and the evidence of viral reactivation.

Other contributors to this issue of "Physicians' Forum" who provided their expertise on the diagnostic approaches to ME/CFS included James Jones ("**Unfortunately, the group of individuals being given this diagnosis remains quite heterogeneous. Unless a common definition is applied to all patients...the heterogeneity of the population will preclude determination of diagnostic tests**"); Anthony Komaroff ("**Our studies also indicate that two additional tests are elevated more often in patients with CFIDS: immune complexes and immunoglobulin G (IgG)**"); Benjamin Natelson ("**The major lab tests I check are those indexing immunological dysfunction. I do a standard clinical immunological profile, including circulating immune complexes, complement levels and IgG subclasses. I have found a rough correlation between disability and the number of these tests that are positive....being able to report such examples of immune dysfunction is often of practical value in assisting the severely ill CFS patient in obtaining disability**") and Daniel Peterson ("**Often an objective measurement of the fatigue, such as one obtained through exercise tolerance testing with expired gas exchange, will document impaired VO2 utilisation. This documentation often helps to affirm the significance and extent of this aspect of the disease**").

In the UK, all this evidence of serious organic disease fell – and continues to fall -- on the deliberately deaf ears of the Wessely School and hence on the equally deaf ears of NICE, the Medical Research Council and the NHS. Indeed, it was stated at the time that the Wessely School and UK clinicians would never accept the views of "*people like Cheney*" (personal communication).

As recently as March 2011, The British Association for Chronic Fatigue Syndrome/ME (BACME), whose Chair is Dr Esther Crawley (a keen Wessely School supporter and a member of the group which produced the NICE Clinical Guideline 53, and who is currently embroiled in altercations about her desire to use children with ME in her study of the Lightning Process) issued glowing support for the much-criticised PACE Trial, claiming the results provide "*convincing evidence that GET and CBT are safe and effective therapies and should be widely available for patients with CFS/ME as per the NICE guidelines....This trial shows that approaches aimed at staying within limits imposed by the illness are less effective than those that test such limits*". BACME's membership is open only to those UK healthcare professionals and researchers who accept the recommendation of the NICE Guideline 53 (ie. that CBT and GET are the best "evidence-based" approaches to ME/CFS). The Association's objective is "**To champion evidence-based approaches to the treatment of CFS/ME, such as those provided in the NICE guidelines**" and BACME will use "*clinical expertise to inform healthcare policy*" and will "*provide training for clinicians and researchers from all disciplines involved in the diagnosis and treatment of CFS/ME*". Of great concern is the fact that BACME claims it has an "*active training programme*" and "*the ability to provide national training programmes*" about ME/CFS for UK healthcare professionals. As with other adherents to the Wessely School's belief that ME/CFS is a

behavioural disorder, BACME appears systematically to ignore the biomedical evidence proving that ME/CFS is a serious multi-system organic disease whose devastating impact cannot be ameliorated by pretending otherwise.

1992: A Press Release for the Albany, New York, International Clinical and Research Conference on ME/CFS (held on 2nd-4th October 1992) from the Department of Neurology, Institute of Neurological Science, University of Glasgow said: *“We will report...our new findings relating particularly to enteroviral infection. We have now extended our PCR data to cover hundreds of patients together with controls and have continued to find a very significant proportion of the patients’ muscle biopsies to contain enterovirus on PCR. In addition we have used several different types of enteroviral primers and have obtained identical results in the patients with these primers, the control muscle biopsies from healthy subjects and patients with other muscle diseases being entirely negative. We furthermore have isolated RNA from patients and probed this with large enterovirus probes which demonstrated that full length 7.4 kilobase virus was present in these patients. Indeed, detailed studies including Northern Blot analysis showed that the material was true virus....Furthermore, this virus was shown to be replicating normally at the level of transcription. Sequence analysis of this isolated material showed that it had 80% homology with coxsackie B viruses and 76% homology with poliomyelitis virus, demonstrating beyond doubt that the material was enterovirus. We were able to extend these studies...by being able to study post-mortem material from a definite case of chronic fatigue syndrome....This showed that enterovirus was present in skeletal muscle, in heart muscle, but particularly was abundant in brain. Detailed studies of the brain enterovirus revealed that it was most prevalent in diencephalic, particularly hypothalamic, regions. Clinical studies employing dynamic techniques of measuring neuroendocrine neurotransmitter hypothalamic function showed that there was disturbed hypothalamic regulation for neurotransmitters, particularly for 5-hydroxytryptamine and for hormones governing water metabolism in affected patients”.*

1992: Scientists and clinicians at The Albany Conference discussed current concepts in ME/CFS, the epidemiology of ME/CFS, clinical research, viral studies, immunological studies, evidence of mitochondrial dysfunction, abnormal neuroendocrine responses, including defects in central control of respiration (ie. a defect in HPA axis function), evidence from ergometry with gas analysis which proves that patients are truly “weak”, evidence establishing two gene markers that occur frequently in CFIDS patients but not in the general population (persons with HLA Dr4 and Dq1, who collectively represent less than 5% of the general population, were found in 93% of the ME/CFS population tested, and both markers are associated with decreased NK cell activity), ocular manifestations, and public policy, including the economic impact of ME/CFS. A review of the conference was published in The CFIDS Chronicle, Summer 1993. The full proceedings were published in the Journal of Clinical Infectious Diseases 1994:18: S1 (http://cid.oxfordjournals.org/content/18/Supplement_1).

1993: In his now world-famous Testimony before the US FDA Scientific Advisory Committee on 18th February 1993, Dr Paul Cheney said: *“I have evaluated over 2,500 cases....We have seen the*

worst and the best of the range of scenarios that can befall a patient with this disorder. At best, it is a prolonged postviral syndrome with slow recovery or improvement within one to five years. At worst it is a nightmare of increasing disability with both physical and neurocognitive components. The worst cases have both an MS-like and an AIDS-like clinical appearance....We have lost five patients in the last six months....The most difficult thing to treat is the severe pain....The most alarming is the neurological and neurocognitive elements of this disease. Half have abnormal MRI scans, 80% have abnormal SPECT scans, 95% have abnormal cognitive evoked EEG brain maps. Most have abnormal neurologic examinations....40% have impaired cutaneous skin test responses to multiple antigens. Most have evidence of T-cell activation....From an economic standpoint, this disease is a disaster. 80% of the cases evaluated in my clinic are unable to work or attend school...The yearly case production, if plotted, is exponential....The medico-legal aspects of our practice steadily grow as this disease eats at the fabric of our communities. We admit regularly to the hospital (with)...inability to care for self....CFS is an emerging, poorly understood disorder with a distinctive clinical presentation. I am not at all sure that it is as heterogeneous as some would lead you to believe....This disorder is a socio-economic as well as medical catastrophe that will not end....This disease is too complex to rely on standard medical orthodoxy to explain it....Listen to patients with an open mind. Failing that, then listen to those who have spent countless hours with a thousand patients. Most of us have some wisdom to impart and most of that came from patients”.

1993: The Los Angeles conference entitled “The Medical Neurobiology of Chronic Fatigue Syndrome and Fibromyalgia” was held on 7th-9th May 1993 and reported in the Summer 1993 CFIDS Chronicle. Emphasis was again placed upon the importance of brain scans, with the most talked-about technology being the results of Dr Ismael Mena’s SPECT scans (conventional brain scans such as MRI and CT scans look at brain structure over function, but SPECT scanning examines brain function by measuring cerebral blood flow or CBF). Results showed profound dysfunction in CFIDS patients: **“We are seeing a pattern of blood flow that is quite different from the uniform pattern of distribution that we see in the normal individual....CFIDS is characterised by a diminution of CBF and diminished uptake of HMPAO (a radioisotope used to track CBF), primarily in the right hemisphere, extensively involving the frontal and the temporal lobes....The study of CBF and its relationship to cerebral function appears to be a very powerful biological marker for CFS”** (brain imaging for NHS patients with ME/CFS is not available in the UK and requests are refused). The CFIDS article continued: **“Cerebral hypoperfusion is the most common finding in the CFIDS brain, and researchers have associated it with nearly every CFIDS symptom”**. Drs Mena and Goldstein presented a series of SPECT scans **“which showed extreme hypoperfusion in the brain following exercise. There appeared to be ‘holes’ where blood would normally be flowing – the degree of hypoperfusion was astonishing. Even 24 hours later, cerebral blood flow was severely reduced”**. Dr Byron Hyde from Canada said: **“What we’re going to tell the insurance companies from now on is not ME, for which they won’t pay, and not CFS, but major acquired brain dysfunction. And that is what these people actually have”**.

Other researchers drew attention to the presence of vertigo in patients with ME/CFS (caused by a viral condition of the inner ear called endolymphatic hydrops, which is *“probably the result of the reactivation of viruses caused by the dysregulated immune system”*, according to Dr Samuel Whitaker from UC Irvine); to a central defect in the HPA axis that *“prevents the immune system from shutting down, and results in constant immune activation which makes people with CFIDS feel sick”* according to Dr Anthony Komaroff from Harvard. Drs Lapp and Goldstein noted a particular irregularity in tidal volume in CFIDS patients (***“This phenomenon has never been described before in any population and...we think that it’s a diagnostic marker for CFS”***). The Cheney-Lapp study showed that neuroendocrine responses were often reversed or blunted; Drs Lapp and Sietsema reported that people with CFIDS reached anaerobic threshold much sooner than predicted (the point at which a healthy person becomes completely fatigued and cannot exercise any longer, known as *“hitting the wall”*); Dr Byron Hyde explained that what he called *“a perfect virus”* is one which can live and propagate indefinitely in the host without detection, and that *“this infection would produce the immune activation which is responsible for many CFIDS symptoms. ‘As long as the cell is at rest...it can do what it wants. As soon as you put it under stress, under work – whether it’s cognitive work or physical work or sensory work makes no difference – that cell doesn’t function’ ”*.

A major section of the conference addressed the immune defects in CFIDS patients: ***“Up-regulation of the immune system has been well-documented in the CFIDS literature....That this immune activation is responsible for many CFIDS symptoms has been accepted by most researchers and physicians”***. Dr Catherine Rivier from the Salk Institute in La Jolla, California, said: ***“Stress in any form places undue pressure on the immune system....In a normal immune system, interleukin (IL-1) is produced in response to stress. In CFIDS, IL-1 may be obstructed, resulting in a blockage of corticotropin releasing factor (CRF), an immunosuppressor. If CRF is not released, the immune system will remain activated indefinitely”***. Dr Nancy Klimas said: ***“There is considerable question whether all CDC-defined CFIDS patients are suffering from the same disorder....In a normal population, 20 percent of lymphocytes are active at any given time. In CFS, up to 80 percent of the cells are working....These lymphocytes and cytokines are so up-regulated that they cannot be driven any harder. It is as if they have been pushed as far as they can go and the immune system is completely exhausted”***.

1993: The Summer 1993 issue of The CFIDS Chronicle Research Update also devoted much space to the finding of a retrovirus by Dr Elaine DeFreitas. The issue documented the stringency of Dr DeFreitas’ research, her willingness to share data and primers with the CDC, her offer to travel to Atlanta at her own expense to conduct side-by-side experiments using the same patient and control samples, the CDC’s refusal to participate in such collaborative studies with her, their damning dismissal of her work showing the presence of a retrovirus in ME/CFS and their apparent inability to replicate her results. It was noted that ***“certain scientists appear eager to discount any possibility of a retrovirus with CFIDS”***.

The same issue carried a referenced article by Dr Paul Cheney in which he noted the evidence of metabolic disorder in ME/CFS: *“CFS patients demonstrate low oxygen consumption, early transition to anaerobic metabolism, disordered fat metabolism and sweet cravings which fit well into a picture of mitochondrial dysfunction....Evidence of liver dysfunction has recently been observed in most CFS cases. Liver dysfunction would explain the medication and chemical sensitivities so common to CFS. Gut dysfunction, especially increased gut permeability, is presumed to be the basis of cellular energy deficiency and is common to CFS. This would compound the effects of liver dysfunction and could also explain such diverse complaints as food sensitivities or allergies, irritable bowel syndrome, chronic nausea and arthralgias....Reduction in cellular ATP would profoundly affect cellular active transport systems....Electrolyte and mineral gradients would decline and result in further loss of critical cell functions. Intracellular magnesium deficiency reported in CFS would be one of the many examples of this phenomenon....Most interesting of all, liver dysfunction as well as central nervous system mitochondrial dysfunction could explain the subacute encephalopathy so common to CFS. Indeed, cognitive-evoked computer brain maps of severely ill CFS patients are entirely consistent with a metabolic encephalopathy including that seen in hepatic encephalopathy....CFS patients crave carbohydrates (but) if they eat fat, they cannot consume it in the mitochondria, due at least in part to acylcarnitine deficiency, and therefore fat storage increases, as does body weight. Serum cholesterol and triglycerides rise in some individuals. An obvious approach would be to reduce fat intake and raise carbohydrate intake....The loss of excess intracellular minerals such as magnesium due to reduced cellular ATP and subsequent reduced active transport is a special problem....Cardiac function, as well as muscle function in general, may also be profoundly affected by intracellular magnesium deficiency”.*

1993: In The CFIDS Chronicle Physician’s Forum, Fall 1993, Dr James McCoy from Louisiana wrote: *“Chronic fatigue and immune dysfunction syndrome (CFIDS) has been shown to have an associated immune disorder that may be the result of an acquired immunodeficiency....A dysfunctional immune system may be related to the failure of other organ systems frequently observed in CFIDS....Some CFIDS patients produce very low levels of DHEA (dehydroepiandrosterone, a naturally-produced hormone and a precursor of oestrogen and testosterone in humans....Many CFIDS patients are very sensitive to medications and do not tolerate normally-recommended dose levels. Many drug agents, including DHEA, are toxic to CFIDS patients’ lymphocytes at routinely-prescribed dose levels”.* The same Chronicle devoted considerable space to the issue of multiple chemical sensitivity (MCS) in people with CFIDS (ME/CFS): *“...some chemicals are more likely to cause MCS than others. These include dry cleaning fluids, car exhaust, pollution, solvents, paints, new carpet, perfume, smoke, fire, drugs, organic and inorganic chemicals. Commonly seen pollutants which may cause brain dysfunction include acetone, trichloroethylene and chlorinated hydrocarbons”.* **Two important points were made in that issue of Physicians’ Forum; Dr Robert Sinaiko from San Francisco mentioned something that is very common but frequently dismissed by uninformed physicians: “Many CFIDS patients experience lower right abdominal pain, which (Sinaiko) hypothesises is mycotic mesenteric adenitis, an inflammation of the lymph nodes in the abdomen as a result of immune activation”,** whilst Vicky Carpman pointed out: *“Autoimmunity is commonly seen in CFIDS....Once an autoimmune condition begins, it cannot be reversed”.*

Despite the irrefutable evidence that ME/CFS is an organic disease, the Wessely School continue to reject it and seem unable to tell the difference between basic science and doctrine; they are certain that their beliefs about ME/CFS are correct and that it is a somatoform disorder.

One UK consultant physician described their arrogance as “*breath-taking*” and referred to them as “*convinced tub-thumping fundamentalists with no self-awareness*”, pointing out that whilst their mind-set demands proof and scientific certainty before they will accept ME/CFS as an organic disorder, in their own discipline of psychiatry there is no proof or scientific certainty, as a psychiatric diagnosis is dependent upon an individual’s opinion and interpretation, which is an illogical position to uphold.

Given the biomedical evidence outlined above, it is extraordinary if not incomprehensible that the Wessely School persists in its irrational rejection of this evidence.

(To be continued)