"Grey" Information about ME/CFS Part 3: 1994

Margaret Williams November 2011

Part 1 of these extracts from the grey literature on ME/CFS from 1956 – 1990 can be seen at:

http://www.margaretwilliams.me/2011/grey-information-on-me-part-1april2011.pdf

Part 2 of these extracts from 1991 – 1993 can be seen at:

http://www.margaretwilliams.me/2011/grey-information-on-mecfs-part-2_5may2011.pdf

1994: In its issue of Winter 1994 (ie. early 1994), the CFIDS Chronicle reported on meetings in September 1993 at the CDC and on a two-day workshop held in November 1993 at the NIH on the clinical management of ME/CFS. Dr Dedra Buchwald listed commonly reported symptoms not included in the case definition, notably shortness of breath, unsteadiness, morning stiffness, blurred vision and dizziness, and she noted the presence of multiple chemical sensitivity. She stated that *"improvement may represent an accommodation of limitations rather than a disappearance of symptoms"*. Dr Anthony Komaroff provided a review of the respiratory, neurological, rheumatic and gastro-intestinal symptoms of ME/CFS, and emphasised that he did not find that ME/CFS patients over-report symptoms that are not common to the illness. Dr Jonathan Rest reminded clinicians that patients are usually more sick than they appear. Dr Paul Goodnick noted that CFS patients go to great lengths to help themselves, unlike patients with classic depression, and made an appeal to change the name of the disease, stating that this single act would greatly enhance physicians' understanding of the seriousness of the illness. Seemingly dismissive of the biomedical evidence of expert clinicians, psychiatrist Dr Michael Sharpe contended

(i) that he could potentially cure CFS with CBT; (ii) that factors correlating with worsening of the illness include a belief that it is caused by a viral infection and by belonging to a self-help group, and (iii) that those who do not improve with CBT may have a personality disorder. Dr Phillip Peterson questioned the merit of trying to change patients' beliefs about the disease when the mechanisms of it were not yet known, saying he had found no other disease with such global immune disturbance.

1994: On 14th May 1994 The New Scientist published an article by Renee Twombly (The trouble with ME: New Scientist, Volume 142, No: 1925) drawing attention to a forthcoming conference on

ME/CFS to be held in Dublin that month and noting that it was one of the few conferences on ME/CFS to be held outside the US. Twombly quoted Peter Behan, Professor of Clinical Neurology at the University of Glasgow: "*Behan says that several papers to be presented at the conference offer new evidence that the illness is due to factors that upset a cell's production of energy…. 'All this evidence tells us that the mitochondria are sick in the CFS patients we studied', Behan explains….Behan believes that more support for his theory is provided by work at the University of Leeds, which suggests that muscle cells in patients with CFS contain inadequate supplies of the ions they need for the production of ATP. They also found low levels of phosphate, which is involved in the production of ATP".* Twombly mentioned the views of Dr Keiji Fukuda of the CDC (whose case definition was published that year in the Annals of Internal Medicine) and Dr Peter Manu (Director of Medical Services at Hillside Hospital, New York), noting that Fukuda *"is not ready to accept Behan's theories (and) his unwillingness to exclude psychological factors mirrors the primary position of the National Institutes of Allergy and Infectious Diseases"* and that Manu *"doesn't need any convincing that CFS has a psychological component….Behan, however, dismisses any idea that CFS is controlled by the mind (and) sees dangers in following the psychological approach: 'It's absolutely retrogressive to suggest that CFS is in the heads of patients', says Behan. 'I have seen patients commit suicide, or have been otherwise destroyed, because some professor has diagnosed them as having a psychiatric illness' ".*

1994: The International Meeting on Chronic Fatigue Syndrome was held in Dublin on 18th-20th May 1994 under the auspices of the World Federation of Neurology. It was reported by the ME/CFS charities: in its newsletter InterAction No: 16, the charity Action for ME (AfME) published a report on the conference by Dr Anne Macintyre and Doris Jones (who noted that the meeting was attended by about 170 delegates from Europe, North America, South Africa and Australia), and Stephanie Woodcock of the ME Association reported on it in two issues of its magazine "Perspectives" (in June and December 1994).

There were 24 poster presentations and 46 verbal presentations, including those by Dr Anthony Komaroff from Harvard Medical School, Boston, (who spoke on case definitions); Dr Paul Levine from the National Cancer Institute, Maryland (the history and epidemiology); Dr Irving Salit from the University of Toronto (precipitating events); Professor Ted Dinan from London (the neuroendocrinology of the disease); Dr Charles Poser from Harvard (the differential diagnosis between ME/CFS and MS); Dr Frances Aitchison from Glasgow (brain scans on ME/CFS patients); Dr Jay Goldstein from California (cerebral blood flow [CBF] by SPECT scans); Dr Russell Lane from Charing Cross Hospital Medical School, London (defective muscle metabolism and the presence of enterovirus RNA in the muscle); Dr Wilhelmina Behan from Glasgow (mitochondrial changes); Dr Hirohiko Kuratsune from Osaka University, Japan (acylcarnitine deficiency); Dr T Majeed from the Department of Neurology, University of Glasgow (who also spoke on abnormal intracellular acylcarnitine); Dr Layinka Swinburn from the Department of Chemical Pathology and Immunology, St James University Hospital, Leeds (insufficient ATP and the consequences); Professor Andrew Smith from the University of Bristol (abnormalities in objective measures of cognitive impairment), and

Professor Dr Rainer Ihle from Dusseldorf (immunological changes, hormonal disturbance and increased levels of toxins, and on myocardial SPECT scans). Drs Fukuda and Peter White also gave presentations, Dr White's talk referring only to patients who were fatigued after proven glandular fever.

Notable points made in 1994 which 17 years later have still not entered mainstream medicine (due largely to the influence of the Wessely School) include the following:

Dr Anthony Komaroff said that symptoms which are not currently part of the case definition such as anorexia, nausea, alcohol intolerance and parasthesaias may be added to a revised case definition.

Dr Paul Levine from Maryland warned that *"CFS is not one disease, and your diagnosis may depend on who you see and where – a neurologist's or psychiatrist's group of patients are not going to have the same sort of CFS as those of a rheumatologist"*. He said that ME/CFS is *"an unusual and inappropriate immune response"*.

Dr Jay Goldstein from Los Angeles had done hundreds of brain scans on ME/CFS patients and reported that SPECT scans show obvious abnormalities. He said that the overall patterns of rCBF (regional cerebral blood flow) were distinctly different in depression compared with CFS, and that patients with (ME)CFS who have co-morbid fibromyalgia have more severe hypoperfusion than patients with (ME)CFS alone. He said it is possible to differentiate (ME)CFS from depression by looking at the hypoperfusion pattern (in 2011 in the UK, scans to aid diagnosis of ME/CFS are still proscribed by the NICE Clinical Guideline 53, again due to the influence of the Wessely School who insist that ME/CFS [or "CFIDS", or "CFS/ME" or "CFS"] is a behavioural disorder).

Dr Frances Aitchison, a radiologist from Scotland, said that she had performed both MRI and SPECT scans on ME/CFS patients and that the abnormalities related to areas of hypoperfusion (ie. low oxygenation levels); the areas are principally in the temporal lobes, occipital lobe and the left frontal lobe and these abnormalities are statistically significant.

Dr Russell Lane, a neurologist from London, reported on exercise studies done by his group and said that 32% of (ME)CFS patients tested had abnormal SATET responses (sub-anaerobic threshold exercise testing) suggesting defective muscle metabolism and 21% were positive for enterovirus in muscle; there was a significant association between abnormal SATET and enterovirus (being greatest in patients with a greater lactic acid response to exercise). Heart rate response to exercise, as well as muscle fibre morphometry, showed these abnormal lactate responses could not be due to deconditioning: he stressed that morphologically, most of the (ME)CFS patients had muscle

hypertrophy, whereas unused or deconditioned muscles would be expected to show atrophy. He concluded that a significant proportion of ME/CFS patients have evidence of impaired aerobic muscle function.

Dr John Gow from Glasgow reported that evidence of enteroviral sequences can be found in the muscles of up to 82% of (ME)CFS patients and that the persistence of a virus may upset cell homeostasis.

Dr Wilhelmina Behan from Glasgow said that electron microscopy has shown abnormalities of mitochondria: enlargement, change of shape and proliferation of cristae, giving an abnormal honeycomb appearance, was found in up to 70% of muscle biopsies (the abnormal mitochondria were about twice the size of normal). The structure of mitochondria is very closely linked to energy metabolism and Dr Behan concluded that the findings suggest an interference with energy metabolism. Cell cultures were established from 10 muscle biopsies and severe decrease in cell respiration was found in two of the four samples tested. Serum acylcarnitine is deficient in CFS patients. A mtDNA deletion was found in four patients but in none of the controls. These data on mitochondria suggest that CFS may be precipitated by environmental factors in individuals who are genetically predisposed.

Professor Dr Rainer Ihle from Germany said that data on 375 CFS patients demonstrated various immunological changes and autoantibodies (especially antinuclear antibody and microsomal thyroid antibodies) in an abnormally large proportion of CFS patients, suggesting impaired immunity and facilitating transition to autoimmune disease ("*On the basis of these immunological serological and organ-specific findings, which affirm previously published results, it would appear that the organic nature of the pathogenesis of CFS has now been demonstrated"*). He also found vitamin and mineral deficiencies, hormonal disturbances, and increased levels of toxins such as wood preservatives and pentachlorophenol. SPECT scans showed reduced rCBF in 83%, and MRI scans showed focal changes in 30%. SPECT scans of the myocardium showed conspicuous changes in 73% during exercise. Professor Ihle reported that 75% of his cohort experienced dizziness and 53% had hair loss. He said that future studies should differentiate subgroups of CFS, which would improve targeting of therapies (this should be compared with the Wessely School's insistence that there is no need for subgrouping and their intention to classify all states of medically unexplained "fatigue" as a somatoform disorder).

Dr Layinka Swinburne from Leeds confirmed that the distinct symptom of ME is fatigability of muscle after minimal exercise, with slow recovery before muscle power is restored, and said thatDr Melvin Ramsay called this phenomenon the 'sheet anchor of diagnosis'. She presented evidence that the basis of the fatiguability is a defect in the regeneration of high energy phosphates, especially ATP, and that such an impairment would generate changes in membrane bound transport and ion movement, leading to chronic intracellular ion depletion (phosphate, potassium and magnesium),

with further impairment of mitochondrial function; physical activity would produce greater depletion, leading to interference with many other functions such as immune reactions, hepatic detoxification, gut motility, neurotransmitter function, maintenance of red cell shape and tissue respiration.

Dr Sean Coyle, an associate of Dr Swinburne, noted that serum potassium and phosphate levels have been shown to be decreased in ME and that renal tubular handling of phosphate was low, suggesting an inappropriate loss of phosphate in patients with ME. He noted that low phosphate levels could affect every cell in the body and may cause bone factures, weakness, fatigue, abnormal pulmonary function, low blood pressure and depressed cardiac stroke volume, as well as cognitive dysfunction.

Dr Jay Levy from San Francisco presented serological and immunological data from (ME)CFS patients, pointing out that, by lymphocyte phenotype analysis, the T8 suppressor subset was decreased, a notable and important finding, since others have found the opposite (perhaps due to the heterogeneity of subjects). He also found that activated T cells were increased, with the most pronounced increases seen in the sickest patients, and that NK cell activity and cytotoxic lymphocyte activity were both depressed in (ME)CFS patients.

Dr Hirohiko Kuratsune from Japan expanded on his 1992 presentation at the Albany, New York; he found in a Japanese study that most (ME)CFS patients – male and female -- had serum acylcarnitine (AC) deficiency, and that the degree of AC deficiency related to the severity of the symptoms; no

AC deficiency was found in bed-rest patients without (ME)CFS, implying that low AC in (ME)CFS is not due to physical deconditioning. He pointed out that the sicker patients have lower AC levels. There was no urinary increase in AC, thus the deficiency could not be attributed to urinary loss. Perhaps unfortunately, AC levels are not specific for (ME)CFS as they also occur in infection, malabsorption, AIDS and other immune dysfunction syndromes.

Dr Charles Poser from the US, an internationally renowned neurologist specialising in MS, found similar brain lesions in both ME/CFS and MS patients, suggesting a chronic and recurring brain disorder. In his view, the fatigue in both disorders is indistinguishable. He reported authoritatively that atypical reactions to many different medicines and drugs is virtually pathognomonic of ME/CFS.

Professor Ted Dinan from London reported on abnormal neuroendocrine findings and said that the pattern of neuroendocrinological response appears to be unique in ME/CFS patients, with an enhanced prolactin (an important stress hormone) response when challenged by the anti-anxiety

drug buspirone, and a blunted response to dexamethasone, with ME/CFS patients having lower baseline GH (growth hormone) levels than either normal controls or depressed patients.

Professor Andrew Smith from Bristol said that over 5 or 6 years he had demonstrated significant impairments of motor function and abnormalities on objective measures of memory and attention, and that central nervous system functioning is definitely abnormal in ME/CFS patients.

Professor Mark Demitrack, a US psychiatrist, reported that patients with major affective disorders tend to have hypercortisolism, whereas patients with (ME)CFS have adrenal insufficiency (ie. hypocortisolism), with a 30% drop in overall cortisol output. He concluded that "*(ME)CFS patients cannot be absorbed into any one pre-existing psychiatric diagnostic category"*.

The Dublin meeting was an important international conference but apart from derisory comments in the medical trade press, it received almost no mention in the mainstream media or medical journals.

The medical trade press was factually incorrect and scathing; "GP Medicine" carried an article by Paul Haines with banner headlines proclaiming: "*Research fails to impress"*, which went on to disparage the entire conference: "*In Dublin last month, when the city hosted the first world conference on myalgic encephalomyelitis* (this was incorrect – the first World Symposium on ME was held four years previously in April 1990 at the University of Cambridge)*, one old woman claimed to know the condition's origin…Her point of view was only slightly less conventional than many of the other theories that were expounded at the conference…The American presence was enormous, reflecting the enthusiasm with which that country has embraced the subject of ME. Three or four delegates carried video cameras to record each other….Each speaker presented his pet theory with some research data to back it up. But once the talk was over….there seemed little lasting interest….There were countless presentations about viral triggers and neuro-endocrine activity"*.

Despite the biomedical evidence that was presented, the article erroneously asserted: "*Disappointed doctors are none the wiser after ME conference".*

In the "Medical Matters" section of its magazine "Perspectives" (September 1994) the medical advisor to the ME Association, Dr Charles Shepherd, wrote: "*Sadly, the conference failed to achieve very much publicity in the medical press. Having personally contacted the editors of most of the mainstream medical journals, it was very disappointing to find little or no coverage being passed on to a wider medical audience".* Commenting on an Editorial in GP, Dr Shepherd said that it "*appeared to be written by someone who has an extremely biased view of the whole ME debate. Titled 'Doctors can be right too', the editorial went on to describe, quite inaccurately, a meeting attended by*

'hundreds of hangers-on' and papers being presented by 'those who measured and pampered the afflicted' ".

(Later that same year, on 20th November the Sunday Telegraph reported on a conference attended by 150 British psychiatrists held on the island of Jersey, proclaiming: "*ME is just a myth….A group of leading psychiatrists has overwhelmingly concluded that ME is all in the mind*").

1994: The Spring 1994 issue of the CFIDS Chronicle carried an article by Dr Paul Cheney of Charlotte, North Carolina, on the likely pathophysiological mechanisms underpinning ME/CFS, in which he drew attention to key symptoms. These most commonly include…subnormal temperature; myalgias (especially of axial skeletal muscles); deep bone pain in the extremities; arthralgias; pressure headaches; sleep disorders; enlarged and/or painful lymph nodes; night sweats; new onset or worsening of allergies; dizziness or balance problems; migrating sensory dysesthesias; sensitivities to heat, cold, light, sound and chemicals; alcohol, food and drug intolerance; visual disturbances; disabling cognitive impairments; acneform, herpetiform and morbilliform skin eruptions, and an assortment of breathing, cardiac, gastro-intestinal and genitourinary symptoms.

Amongst the most common physical findings (ie. signs detectable by a clinician) are palpable, slightly enlarged discoid-shaped and tender posterior and middle cervical lymph nodes, which are almost always left-side predominant. This left-sided predominance and lymphatic channel tenderness extending into the medial supraclavicular area strongly suggests increased lymph production – lymphatic fluid carries cytokines, and in an immune activation state, lymphatic flow increases, causing fluid retention and tissue oedema commonly seen in ME/CFS which would produce lymphatic congestion (over 90% of lymph flows back into the blood stream just below the left collar-bone, so if there is increased flow, congestion will occur within lymph node chains closest to that juncture, hence left-sided dominance of lymph node tenderness in the supraclavicular area).

Other common physical findings include a higher than normal incidence of hyper-reflexia (80% of patients) and abnormalities of vestibular function with an inability to maintain the Romberg, tandem or augmented tandem stance positions (which clinically support the evidence of central nervous system injury observed on functional and structural brain scans).

In an interview with Dr Cheney published in the same issue, he said that ME/CFS patients have limited anti-oxidant reserve, and this is why exercise sends them into relapse.

The same issue carried an article by Dr Nancy Klimas et al reporting on the association between HLA (histocompatibility locus antigen) Class II antigens and CFIDS/ME/CFS. Klimas noted that her group and others have reported a strong association between immune dysfunction and a serological viral reactivation pattern in these patients similar to that observed in conditions such as chronic active hepatitis and systemic lupus erythematosus in which a definite association between a particular HLA-DR/DQ haplotype and increased disease frequency has been reported. Her data suggest that DR4 and DR5 are associated with an increased risk of developing CFIDS/ME/CFS and that it may be triggered in such people by various stimuli, resulting in a state of chronic immune dysequilibrium. This would easily explain the findings with regard to acute viral infections, chronic active viral infections and allergies in these patients.

In an article titled "Dancing with the serpent", Tara Allan wrote: "*It's hard to believe that people are still so uninformed about the severity of this illness, but it's true"*. When someone challenged her by telling her "*If you believe, you can get well"*, she dared that person to walk a mile in her shoes before he could tell her how to live, saying: "*In the end, each person copes to the best of his or her own ability. No-one has the right to make you or me defend the fact that we are ill. That is completely unacceptable and incredibly cruel".*

1994: The Summer issue of CFIDS Chronicle carried an important article by Professor Paul Cheney explaining exactly why the 2'-5' A / RNase L pathway is so important in (ME) CFS: noting the clinical impression that patients suffer from a chronic viral infection, Cheney stated: *"Perhaps the strongest evidence that (ME)CFS may be due to a persistent viral infection is the strong activation in (ME)CFS patients of a principal anti-viral pathway. The 2'-5' A synthetase/RNase L pathway is the most important intracellular antiviral defence mechanism in mammalian cells….It is initiated by alpha interferon expressed by activated T cells.*

"The alpha interferon binds to receptors on the surface membranes of most cells in the body. This receptor binding results in the expression and activation of 2'-5' A synthetase, which converts ATP (a source of energy) to bio-active 2'-5'-oligoadenylates (2'-5' A). Ultimately, this pathway activates RNase L…to degrade human and viral single-stranded RNA.

"Significant activation of RNase L would substantially disrupt cell metabolism and energy production and beyond that, organ and body function.

"Hormonal action in the body would also be substantially disrupted by activation of RNase L. A clinical situation could arise in which patients appear to be hypothyroid or hypocortisolaemic, based on clinical signs and symptoms, even though their actual hormone levels were normal.

"Disruption of messenger RNA by RNase L would, in effect, functionally decapitate hormone function at the cellular level.

"This problem would not necessarily respond to hormone therapy, even if the patient clearly had clinical evidence of hypocortisolaemia or hypothyroidism.

"Additional cell functions could be affected including the production of neurotransmitters within the brain, detoxification enzymes within the liver and digestive enzymes within the GI tract.

"In other words, there would be a 'brown-out' of organ function and body systems. The action of RNase L could explain the myriad organ system problems seen in (ME)CFS and could well be the cause of the severe and debilitating fatigue in this disorder.

"Alpha interferon, in addition to activating the 2'-5' A / RNase L pathway, could cause specific injury to …the brain. Alpha interferon is known to be a potent neurotoxin acting though them-opioid receptor in the brain to provoke specific neurotoxic injury to deep brain structures.

"Alpha interferon injected into rat brains is known to specifically injure the HPA axis with a resulting decline in corticotropin-releasing hormone (CRH) production. A decline in the HPA axis has been demonstrated in (ME)CFS patients.

Alpha interferon can cause extensive deep brain injury and may be the common denominator in explaining why (ME)CFS and AIDS dementia complexes show almost identical injury to deep brain structures.

"In summary, the alpha intereferon/2'-5'A/RNase L pathway, if upregulated, would cause two problems which are ubiquitous to patients with (ME)CFS: substantial cellular metabolic dysfunction with profound fatigue; and severe neurocognitive problems due to deep brain injury.

"*At this time, activation of the alpha interferon / 2'-5' A / RNase L pathway is the best common denominator to explain why people with (ME)CFS are sick"*.

The seminal work of Professor Robert Suhadolnik et al on the RNase L pathway was comprehensively ignored by Wessely School.

In the "Letters to the Editor" section this same issue of the CFIDS Chronicle, Eileen Marshall and Margaret Williams responded to Dr Simon Wessely's reply to their article published in the previous (Spring 1994) issue entitled "The Views of Dr Simon Wessely on ME: Scientific Misconduct in the Selection and Presentation of the Available Evidence?"

In his reply, Wessely had made claims which, they pointed out, could not be substantiated; furthermore, he had admitted that he does not recognise ME/CFIDS as a distinct entity but includes all people with unexplained chronic fatigue under the label "CFS", therefore it is not known how many of his supposedly cured patients actually had ME as distinct from chronic fatigue. Marshall and Williams wrote: "*It is sadly true (and we believe it can be readily demonstrated) that Dr Wessely has indeed changed the facts about ME, that he has indeed misrepresented the valid findings of other ME researchers and that he does ignore important findings which do not support his own views. Bearing this in mind, we feel justified in querying whether or not this amounts to scientific misconduct".*

Another published letter on the same topic was sent by Richard Sykes, then the Director of Westcare (a small charity that later became subsumed into Action for ME), defending Wessely and asking for the CFIDS Chronicle to print an apology to him for having published the Marshall and Williams article and stating "*Failure to achieve balanced views is not a crime, nor does it imply professional misconduct"*. The editors' published reply to Sykes was notable: "*We believe that the authors of this article made articulate arguments when drawing their conclusions. You maintain that one-sided views are common and acceptable in science and medicine and, in so doing, you seem to miss the authors' point. How has Dr Wessely reached his 'one-sided view'? With an open mind, honest investigation and authentic use of the scientific method? The authors contend not. And, if they are correct, he may indeed be guilty of scientific misconduct".*

1994: the Fall issue of the CFIDS Chronicle published questions and answers in the section "Ask the Doctor". One such was the reply provided by Professor Anthony Komaroff from Harvard, who is also Chief of the General Medicine Division at Brigham & Women's Hospital, Boston, as well as leading a research team for one of the three NIH-funded CFS Co-operative Research Centres. In reply to the question "*Why do (ME)CFS patients tend to relapse after exercise?"*, Komaroff was clear: *"this is due to an unusual reaction of the immune system to exercise".* He went on to explain that: "*Research groups around the world continue to report that the (ME)CFS patient's immune system*

seems to be in a chronically stimulated state, as if it is engaged in a battle against something it perceives as foreign to the body. Even though the immune system is often in a chronically-stimulated state, some parts of the system seem not to be working very well --- perhaps because they have been working too hard". In reply to the question "*Is there any evidence that (ME)CFS is caused by an infectious agent?"*, Komaroff stated: "*In my judgment, the leading candidates continue to be enteroviruses, herpesviruses…and retroviruses".*

In an article titled "Immune Dysfunction in CFIDS: Why You Feel the Way You Do", Dr Robert Keller from the Centre for Special Immunology, Miami, explained: "*Most chronic states of immune dysfunction have, as a necessary requisite, a genetic component. This genetic 'failing' occurs in a region known as immune response genes, or the HLA system….recent evidence suggests that CFIDS shares this genetic quirk with other chronic immune activation disorders such as systemic lupus erythematosus (and) chronic active hepatitis.*

"Whatever the nature of the trigger….in CFIDS, as in all states of chronic immune activation, the initial presentation of the insulting agent to the cells of the immune system precludes its initial destruction or its effective control. As a result…the immune system remains unbalanced as it tries, albeit unsuccessfully, to rid the body of the insulting agent. A major consequence of this unbalanced condition is the persistent production of powerful cytokines. At some point, this continuous production exceeds the ability of the body to inactivate them. This, in turn, results in their systemic dissemination and a variety of unpleasant consequences….The ability of these cytokines to interact with receptors that are involved in central nervous system control creates many other untoward results. It is now recognised that the brain, the endocrine system and the immune system represent an inextricably linked triad. Imbalance in any one of these 'linked' systems, therefore, will result in obligatory disturbances of the other two".

1994: A four-day International Research and Clinical Conference co-sponsored by the American Association for Chronic Fatigue Syndrome (AACFS) was held in Ft Lauderdale, Florida, on 7th–10th October 1994; it was also sponsored by the NIH, the CDC and the University of Miami. It was reported in the UK ME Associations' magazine "Perspectives" in March 1995 and in the CFIDS Chronicle in January 1995 (from which some of these comments are taken with grateful acknowledgement).

Of the 475 conference participants, nearly half were clinicians and researchers.

The key-note speech was given by Dr Philip Lee, then US Assistant Secretary for Health, who spoke of his recognition of the problems caused by (ME)CFS and of the need for partnership between

governments, researchers, clinicians and patient groups: "*The result is a shared vision in which science is influenced -- rightfully so – by clinical experience and patients viewpoint".*Sadly, such collaboration still does not exist 17 years later, especially in the UK.

The Conference was in two parts, these being the research section held on 7th – 9th October 1994 and the clinical section held on 9th and 10th October 1994.

Knowledge about ME/CFS that was available in 1994 includes the following:

Dr James Jones of Denver, Colorado, reported on exercise capacity testing and the finding of reduced exercise capacity, including abnormal muscle strength and higher than expected heart rate, as well as high lactate levels in (ME)CFS patients.

Dr J Vercoulen from Nijmegen found that patients with (ME)CFS had significantly lower levels of physical activity then healthy controls and that these were similar to patients with MS.

Dr Alison Mawle from the CDC reported that patients with (ME)CFS suffer from higher rates of allergy-related symptoms than normal controls and these were present in 70% of patients investigated.

Dr Adrienne Bennett from Brigham & Women's Hospital, Boston, measured transforming growth factor beta (TGFb) and found that it was elevated in (ME)CFS patients, which might reflect the body's attempt to down-regulate an over-active immune system.

Dr Roberto Patarca (an immunologist from the University of Miami) pointed out that there was growing consensus that many of the viruses observed in (ME)CFS may not be relevant to the aetiology but nonetheless relevant to the pathology that is seen. He proposed that the research community start redefining the CDC criteria for (ME)CFS.

Dr Richard Lanham of the State University of New York at Buffalo reported a very high frequency (stated as 100%) of eye complaints amongst (ME)CFS patients studied. Post-onset symptoms included photosensitivity; photophobia; sensation of foreign body in the eye; blurry vision; abnormalities of peripheral vision; trouble reading; ocular pain; headache; floaters; double vision; itchiness and hazy vision (some of which could be due to fatigue of the eye muscles). Problems seen

on ophthalmic examination included narrowed arterioles; retinal defect; fibrillar changes in the vitreous; peripheral cystoid degeneration; drusen; pigment changes; chorioretinal macular abnormalities; pavestone degeneration and optic pallor (this being indicative of neurological disease). Examination of the patients found that 38% had abnormalities of the fundus; 50% had inflamed eyelids and 41% had other pathologies.

Dr Lanham also reported that a significantly greater number of patients than controls had a family member with an autoimmune disease (65% versus 21% of controls).

He further reported that (ME)CFS patients have stiff RBC (red blood cell) membranes like those seen in end-stage renal disease patients, and that this may represent a unique marker for (ME)CFS: *"(ME)CFS patients' stiff RBCs 'may not traverse nutrient capillaries well, resulting in cellular hypoxia…this defect may be part of a more extensive membrane abnormality' which may affect neurons and other cells, leading to additional symptoms"* (it is notable that there is now clear evidence of disrupted biology at cell membrane level and of abnormal vascular biology, with disrupted endothelial function in both large and small arteries, pointing to increased cardiovascular risk for people with ME/CFS – Int J Cardiol 2011:doi:10.1016/j.ijcard.2011.10.030).

Dr Daniel Clauw from Georgetown University Medical Centre, Washington, discussed the relationship between interstitial cystitis (IC) and (ME)CFS: "*IC may be yet another disorder which has considerable clinical and pathogenic overlap with FM and (ME)CFS".*

In relation to the overlap between the two disorders fibromyalgia and ME/CFS, Dr Clauw noted the gastrointestinal symptoms and chest pain frequently described by patients (hence the need to use accurate diagnostic criteria, as called for by Dr Patarca).

Dr Lawrence Borish from the National Jewish Centre for Immunology, Denver, measured TNF-a, IL-1, IL-6 and IL-10 (all associated with lethargy and inflammation); they found that TNF-aand INF-a (interferon alpha) were increased in ME/CFS patients but decreased in major depression. Most remarkably, IL-10 was absent in ME/CFS patients (IL-10 is produced by all T-helper cells and is stimulated by TNF-a, the presence of which implies an inflammatory reaction). The absence of IL-10 supports the characterisation of ME/CFS as an immune disorder with a defect in the immune system's ability to suppress the on-going immune reaction.

Dr Adrienne Bennett from Boston measured TFG-b (a suppressor cytokine) in serum from patients with ME/CFS, from those with depression, with lupus and with healthy controls; levels were significantly elevated in people with ME/CFS compared with the other groups. High levels of TGF-

b may be the immune system's attempt to suppress immune up-regulation (whilst some parts of the immune system are down-regulated, others are up-regulated: Dr Joseph Cannon from Pennsylvania State University provided historical and scientific evidence that females are more resistant to infection than males because of an up-regulation of the immune system; however, it is because of this up-regulation that women are more susceptible to autoimmune diseases).

Dr Irving Salit from Toronto General Hospital found that the percentage of CD4 (T-helper cells) was increased in ME/CFS patient compared with chronically fatigued controls who did not meet the CDC case definition for ME/CFS (a finding that is seen in people with allergies). He determined that ME/CFS patients have *"a variety of immunologic abnormalities (including deviations in) immunoglobulins, T lymphocyte subsets and cell mediated immunity".*

Drs Roberto Patarca, Nancy Klimas and Mary Ann Fletcher et al described three groups of ME/CFS patients based on patterns of cytokine dysregulation: (1) dysregulation of TNF-a/bexpression in association with changes in serum levels of IL-1a, IL-4, (soluble) IL-2R and IL-1 receptor agonist; peripheral blood mononuclear cell-associated expression of IL-1b, IL-6 and TNF-b messenger RNA, and T-cell activation; (2) inter-related and dsyregulated expression of soluble TNF receptor types 1, (s)IL-6R and b2-microglobulin, and significantly decreased lympho-proliferative activity; (3) significantly decreased NK cell cytotoxic activity.

Dr Kenny De Meirleir from Brussels studied 149 patients with ME/CFS, categorising patients' functional abilities using the Karnofsky Performance Scale (KS) which scores from 100 (perfectly well) to 0 (dead). 56 ME/CFS patients had a functional ability of less than 65 and 62 scored between 65 and 75. Flow cytometry was used to measure cellular immune status and the majority of immune abnormalities were found in the ME/CFS group with KS scores between 65 and 75. The immune abnormalities included increases in CD3+HLA-DR+ve T cells and an increase in the CD4/CD8 ratio (an increase in this ratio is found in allergies); there was also a decrease in NK cells.

It is perhaps worth recalling that at his Gresham College lecture on 25th January 2006, Professor Simon Wessely admitted that he does not understand immunology, something that he had previously admitted on 28th August 2004 to the Public Inquiry into Gulf War Syndrome, saying: *"A man has got to know his limitations and my limitations are immunology".*

Dr Dharam Ablashi from Georgetown School of Medicine, Washington, DC, found that HHV-6 was highly reactivated in (ME)CFS patients but not in controls. Whilst not thought to be the cause, HHV-6 seems to contribute to the symptomatology.

Other researchers present (including Dr Jan Vercoulen and Dr Gijs Bleijenberg from The Netherlands) were unable to demonstrate a role for the reactivation of EBV in (ME)CFS patients.

Dr Daniel Hamilos from the National Jewish Centre for Immunology, Denver, demonstrated abnormalities of the autonomic nervous system in (ME)CFS patients compared with depressed patients and normal controls and he suggested that this was further evidence for distinct patho-physiologies in (ME)CFS and depression.

Dr Daniel Clauw from Washington, DC, looked at inflammatory symptoms of the upper respiratory tract and bladder, postulating that central nervous system hyper-activity leads to 'neurogenic inflammation', this being an inflammatory response mediated by the release of neuropeptides such as Substance P and that this increased level of Substance P *"came from nerves within the bladder and may be responsible for the irritative symptomatology seen in (ME)CFS and FM"*. Drs Anthony Komaroff and Adrienne Bennet et al concluded, however, that *"despite their clinical similarities, FM and (ME)CFS are characterised by different abnormalities of the somatotropic neuroendocrine axis".*

William Pettibon, MA; LMHC from the Centre for Special immunology, Ft Lauderdale, found that the results of his neuropsychological study reinforced the view that (ME)CFS patients were not malingering; together with Dr Nancy Klimas et al he found specific areas of cognitive dysfunction, including verbal memory; verbal attention/concentration; visual attention/concentration; visual memory; mental flexibility; rate of memory acquisition and in the level of overall cognitive functioning.

Dr Benjamin Fischler from Brussels compared SPECT scans of patients with (ME)CFS versus those with depression and normal controls; cerebral blood flow was significantly reduced in (ME)CFS patients compared with the other two groups. Dr Frances Aitchison from Glasgow presented additional neuroimaging evidence of differences in blood flow in specific areas of the brain from that which she had presented in Dublin earlier in the year, this being the presence of abnormalities not seen in controls, and evidence that these abnormalities correlated with specific symptom severity.

Dr Frank Duffy from Harvard Medical School, Boston, described quantitative electroencephalogram (qEEG) findings in patients with (ME)CFS compared with depressed patients and normal controls. Spike waves were seen in 44% of (ME)CFS patients versus 1.3% of the other groups, most commonly in the temporal region. (ME)CFS patients had significantly more sharp waves and frequent bursts of high amplitude alpha and theta waves in the posterior regions. Dr Duffy suggested that these abnormalities provide indirect evidence of an inflammatory process of the central nervous system, spike and sharp waves being indictations of CNS irritability. Dr Charles Lapp from Charlotte, North Carolina, suggested that EEG neurofeedback (phase reversals, increased slow wave activity,

decreased fast wave activity and an increased amplitude of the brain wave upon cognitive challenge) could serve as a diagnostic marker for (ME)CFS.

Dr E. Pizzigallo from Chieti, Italy, carried out muscle biopsies from the vastus lateralis muscle in (ME)CFS patients and found alterations in the tissue *"compatible with a myopathy of probable mitochondrial origin"*, which might account for the decreased functional capacity of muscles in

(ME)CFS patients. The researchers went on to say: "*even if a mitochondrial damage in the muscles could explain many aspects of (ME)CFS, we can't exclude an analogous damage in the central nervous system to justify the neuropsychological and neuroendocrinological alterations described in the same patients".*

Dr James Jones from Denver reported that maximum oxygen consumption, maximum workload and anaerobic threshold were reduced in (ME)CFS patients, suggesting that cardiac function at maximal exercise may be abnormal in (ME)CFS. He also performed isometric muscle studies in the quadriceps and hamstring muscles which showed that knee flexor fatigue, strength and recovery were decreased when compared to body weight in (ME)CFS patients. He commented that these dysfunctions may be caused by *"deconditioning, intrinsic cardiac disease or abnormality in the vascular supply or metabolism of the muscles in the lower extremities".*

Dr J Vercoulen from the Netherlands compared an assessment of physical activity in 51 (ME)CFS patients, 50 fatigued MS patients and 53 healthy subjects; (ME)CFS and MS patients scored similarly and significantly lower than controls on the actometer worn at the ankle 24 hours daily for two weeks.

(It is interesting to consider why Professor Peter White decided not to use an actometer as an accurate measure of activity at the end of the PACE Trial).

Notable short quotes from the question and answer session of the clinical conference include the following:

Dr Paul Cheney (in response to questions about gastrointestinal symptoms in ME/CFS): *"Many of these patients are immune activated and may have leaky guts. Undigested food protein leaks across the gut and patients develop reactions to it….CFIDS patients seem to have problems with detoxification, which may explain their sensitivity to medications. We are trying to improve liver function to increase tolerance of medications….Certain vitamins, such as antioxidants, make very*

good sense in an immune activated state….A recent study at The Cheney Clinic demonstrated that the sickest patients did not respond well to any therapy".

Dr Anthony Komaroff (responding to the question: "*What causes problems with focusing the eye in CFIDS?"*): "*there may be intermittent dysfunction of the ciliary muscles, which attach to the lens of the eye. If those muscles are not working well, the lens can't adequately change shape and things become blurry".*

Dr Paul Cheney (replying to the request "*Please discuss the neurological aspects of CFIDS"*): "*There is evidence of functional neurological injury in patients with CFIDS as demonstrated by hyper-reflexia, clonus, balance disturbance and brain irritability".*

Dr James Jones: "*I think the SED rate* (the ESR rate in the UK) *can be a fooler. There are a number of individuals who have inflammatory type symptoms, but their SED rate is absolutely normal. The SED rate is an old, non-specific test of inflammation which is dependent on fibrinogen and interleukin-6. But if inflammatory processes are activated in other ways, the SED rate can be perfectly normal…a normal or low SED rate does not exclude an inflammatory illness".*

Dr Nancy Klimas (when asked about the advisability of people with ME/CFS having flu/hepatitis B or live vaccines): *"Personally, I don't use live vaccines in any of my patients with immune disorders".* Dr James Jones added: "*There are very few live vaccines that adults need".*

Dr James Jones (replying to a question about allergies in ME/CFS: "*Is allergy a common denominator?"*): "*Clinically, this appears to be so….There is literature that suggests that allergic patients, when they get sick, have more symptoms and are sicker longer than other individuals".*

Dr Anthony Komaroff: "*ANA* (antinuclear antibody) *tests are abnormal more often".*

Dr Nancy Klimas (replying to the question "*Is there any link between endometriosis and CFIDS?"*): "*I see a higher incidence of endometriosis in my CFIDS patients than in my general clinic patients"* and Dr Anthony Komaroff said: "*We have just done a case-control study…preliminary results indicate that there may be a higher frequency of endometriosis in the CFIDS patients versus the controls".*

Dr Sharon Moss: "*The type of cognitive deficits seen in CFIDS patients are similar to those of aphasia, traumatic brain injury and dementia patients".*

From the Doctor-to-Doctor session: *"The leaders of the session felt that it was extremely important to validate the patient's illness".*

The Wessely School profoundly disagree with such a view: they are on record in 1992 asserting at the CIBA Foundation Symposium on ME/CFS that the first duty of the doctor is to avoid legitimisation of ME/CFS patients' symptoms, a situation that, disturbingly, continues to date in the UK.

The same issue of CFIDS Chronicle in which the Ft Lauderdale Conference was reported also carried an article by Hillary Johnson entitled "A test of Time: Defining CFIDS in Modern and Historical Terms" in which she quoted from Dr DA Henderson's 1956 description of (ME)CFS: "*Terrifying dreams. Crying without provocation. Nausea and headache and diarrhoea….Back and neck pains. Problems of memory and mentation. Vertigo. Hyperventilation. Menstrual irregularities. Difficulty in swallowing. Fatigue. Fast heart…. Paresthesia (transient numbness and tingling). And paresis (extreme muscle weakness)…. We were left with one possibility. It was also, of course, the likeliest explanation….It was probably a virus".* In 1959, Henderson recorded that: *"the courses of the patients have been unaccountably prolonged and debilitating and marked by frequent exacerbations".* Johnson continued: "*Shelokov, today, is confident that (it), CFIDS and what the English and Canadians prefer to call myalgic encephalomyelitis are the same disease: 'This cannot be…psychiatric, or hysteria, or hypochondria, or emotional' ".*

Given what has been known about ME/CFS for so many years, how is it possible for the Wessely School psychiatrists who claim to care for such patients to maintain a fixed position which disregards this body of evidence and to continue to practise their own psychosocial interventions, the efficacy of which is not supported by the published data, including their own?

(To be continued)