EXTRACTS FROM PRESENTATIONS BY Dr PAUL CHENEY

Following the Chronic Fatigue Syndrome National Consensus Conference held on 19th and 20th February 1995 in Sydney, Australia, Dr Cheney returned to Australia in August 1995 to provide a three day intensive workshop for practitioners treating chronic fatigue syndrome (CFS/ ME). These notes are taken from Extracts from Proceedings prepared by Dr Mark Donohoe (*Chronic Fatigue Syndrome Resource Documents).* The full proceedings, including the consensus statement and all the reference papers, can be obtained from The Institute of Functional Medicine, 1 Bradley Avenue, Milsons Point, New South Wales 2061, Australia.
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It is notable that the information set out below (and more) was in the public domain in August 1995, yet was comprehensively ignored or dismissed by a group of UK psychiatrists and like-minded colleagues led by Professor Simon Wessely (an adviser on chronic fatigue syndrome / myalgic encephalomyelitis / Gulf War Syndrome to UK Government Departments and hence to hospital commissioning officers) when they produced the Joint Royal Colleges' Report on CFS/ME fourteen months later in October 1996. In that Report, Wessely et al specifically state the following:

- *"ME" does not exist*
- *patients wish to keep the term "ME" because only with that label are they eligible to call upon the welfare state for help*
- *aims of assessment should be to "elicit the beliefs and fears of patient and family"*
- *the dysfunctional "beliefs" of CFS / ME patients have an important place as an obstacle to recovery*
- *ME/CFS is a somatisation (psychiatric) disorder ("the greater the number of somatic symptoms, the greater the probability of psychiatric disorder")*
- *cognitive behaviour therapy is a cost -effective, safe, beneficial and acceptable treatment*
- *there is no convincing evidence of any change in muscle structure or function other than those secondary to inactivity*
- *there is no evidence to support rehabilitation by "pacing"; the "vast literature" on the adverse effects of rest is emphasised*
- *some people "use the results of immunological tests as evidence for a so-called 'organic' component in CFS (but) such abnormalities should not deflect the clinician from the (psychiatric) approach endorsed below, and should not focus attention….towards a search for an 'organic' cause. There is no compelling evidence linking immune dysfunction with disability"*
- *the link between viral infection and CFS may be a "behaviour change": chronic fatigue following a viral infection is associated with the patient's somatic attributional style (ie. a tendency to see themselves "as suffering from a physical*

illness"), personality and "psychological distress" and with the issue of sick certificates by doctors (in another article, Wessely wrote "Suggestible patients with a tendency to somatise will continue to be found among sufferers from diseases with ill-defined symptomatology…until doctors learn to deal with them more effectively…Uncritical diagnoses may reinforce maladaptive behaviour" Psych Med 1990:20:35-53)

- *there is no reason for the creation of specialist units*
- *self-help literature may have a deleterious effect on patients*
- *complementary therapy, including dietary modulation, is discouraged*
- *antidepressants should be administered, even in the absence of depression*
- *specific guidelines for the management of CFS should not be issued to general practitioners*
- *no investigations should be performed to confirm the diagnosis*
- *children with CFS / ME may need to be forcibly removed from their parents, who may be suffering from "even Munchausen's by Proxy Syndrome"; children should be immediately returned to school*
- *the need for future research is regarded as unnecessary*

The Australian workshop provided in-depth understanding of the causes of CFS and the biological processes involved.

A diagnostic programme has evolved from the workshop, allowing for better categorisation and management of CFS sufferers. The doctors at the workshop have adopted this as a common diagnostic standard.

A historical and clinical perspective on CFS as a guide for future directions

"The history of medicine is a story of amazing foolishness and amazing intelligence" (Jerome Tarshis).

In recent years it has become ever more apparent that a difficult-to-diagnose but clinically recognisable disorder characterised by unexplained debilitating fatigue and other symptoms exists in large numbers in communities across the developed world. Recent studies using defined case definitions have revealed that prevalence rates range from 10 to 1,000 cases per 100,000.

There is also a sense that the numbers of such patients may be increasing. In April 1994, one of the largest disability insurers in the United States (UNUM) reported that in the five years from 1989 - 1993, mens' disability claims for CFS increased 360% and womens' claims for CFS increased 557%. No other disease category surpassed these rates of increase.

In our view, the clinical coherence of these patients surpasses the differing clinical description of similar fatiguing illnesses. We will present evidence of this clinical coherence in a case-controlled study of physical findings.
It is likely that the syndrome we call CFS is both very old and also very new.

What is old is the pathophysiology of post-infectious or post-stressor syndrome which results in a self-maintaining cycle of dysfunction within the locus of injury within the central nervous system. On the other hand, the coherence of these patients and the remarkable rise in cases suggests the distinct possibility that a novel agent or process exists.

There are two challenges before us; one is to elucidate the common pathophysiology of long-term fatiguing illnesses of variable aetiologies and the other is the challenge of reducing most cases of CFS to a single aetiology evident since the late 1970s.

Summary of major points from transcript of presentation

When a thing was new, people said ' It's not true'.
Later, when the truth became obvious, people said 'It's not important'.
And when its importance could not be denied, people said 'Anyway, it's not new' .
(William James (philosopher).

Chronic fatigue syndrome has features of autoimmune disorders (eg lupus), features of allergy and multiple chemical sensitivity (MCS), features of neurological disease (multiple sclerosis) and features of psychiatric disease. The syndrome shares many features of infectious disorders (like HIV) and features of tempero-limbic encephalopathies. The disorder does not fit the definitions of other diseases and probably is a distinct entity.

The CDC Case Definition

The Centre for Disease Control (CDC) case definition now includes a separate diagnostic category for prolonged fatigue which does not meet the necessary criteria for CFS. There is a major problem with the CDC case definition, and that is that five of the eight symptoms relate to pain, so a patient without pain cannot, by definition, fulfill the diagnostic criteria for CFS. This seems incorrect. As well, the diagnostic criteria do not include symptoms of environmental sensitivities or balance problems, which are common in CFS.

The case definition goes on to describe additional information required (termed "essential subgrouping variables"); for physicians to conform to these additional requirements is an onerous task which is not likely to be performed in clinical practice.

Is CFS a New Disease?

The disease seems to have been around for some time, under various names which include

- neuromyasthenia (Beard, 1869)
- myalgic encephalomyelitis / ME (UK, 1950s)
- chronic Epstein-Barr virus / CEBV (Straus & Jones, USA, 1980s)
- post-infectious fatigue syndrome
- low natural killer cell syndrome (Japan)

There have been many published studies of epidemics over the past 100 years, but one wonders if we really are talking about the same illness.

Hallmarks of CFS

Chronic Fatigue Syndrome (CFS), also known as Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) represents a clinical disorder of unknown cause marked by chronic disability and multiple somatic complaints.

Although typically a chronic illness without remission, cycles of severe relapses are common, together with a characteristic evolution of further symptoms over time.

Different patients have different symptoms, but the general pattern or constellation of symptoms (and the evolution of major symptoms) are remarkably coherent when patients are viewed as a group and over time.

The view held by some doctors that these patients usually turn out to have other, more definable disorder is certainly not the case for patients meeting the CDC case definition for CFS.

There are certain hallmarks of the illness currently termed CFS which include:

- abrupt onset in previously healthy individual
- post-exertional fatigue
- alcohol intolerance
- headaches described as “pressure” more than “pain”
- medication and environmental sensitivities
- balance complaints, including dizziness, are striking
- unusual cognitive processes including difficulty with memory sequencing, processing speed, word searching, spatial organisation and calculation

Physical Findings

The signs of CFS are usually not considered, but they include:

- low-grade fever
- low blood pressure (especially neurally-mediated hypotension)
- abnormal oropharynx (crimson crescents on soft palate)
- lymphodynia (tender lymph nodes)
- hyper-reflexia without clonus
- positive Romberg, tandem stance and augmented tandem stance (most CFS patients fall over in these tests)
- destruction of fingerprints (atrophy of fingerprints is due to perilymphocytic vasculitis and vacuolisation of fibroblasts)
- facial vasculoid rashes
- tenderness in left posterior cervical nodes (more prominent of the left due to thoracic duct inlet on the left: immune activation causes increased lymphatic flow, with congestion where the thoracic duct joins the left jugular vein. Tenderness is found in 90% of patients).

Among the most common physical findings in CFS are palpable, slightly enlarged, discoid shaped (as opposed to spherical) and tender posterior cervical chain lymph nodes, which are almost always left predominant and extend into the supraclavicular node area. This left-sided predominance and lymphatic channel tenderness strongly suggests increased lymph production and clinically supports the published reports of immune activation in CFIDS. In an immune activation state, lymphatic flow increases, and an acceleration of lymphatic fluid production would cause fluid retention and tissue oedema. Lymphatic fluid carries protein messages (via cytokines). Anatomically, over 90% of lymph flows back into the blood stream just below the left collarbone, hence the left-sided predominance of lymph node tenderness in the supraclavicular area.

There is a higher than normal incidence (>80% in patients versus 20% in controls) of hyper-reflexia.

There is abnormality of vestibular function (seen in > 90% of patients versus no controls), with the inability to maintain the Romberg, tandem or augmented tandem stance.

Recent studies on CFS patients have demonstrated evidence of a metabolic disorder involving cellular energy production; studies have demonstrated reduced oxygen consumption consistent with a defect in mitochondrial function.

Additional indicators of defects in trans-membrane mitochondrial transport mechanisms have been reported in CFS and related disorders.

Most patients with CFS show evidence of abnormalities in the citric acid cycle intermediated on overnight urine testing using gas chromatography.

Prevalence

Prevalence and incidence have been reported over a very broad range, depending greatly on the selection criteria and type of study undertaken. Rates range from 10 cases per 100,000 (USA, based on CDC definition) to1,000 cases per 100,000 (Harvard Primary Care Clinic based on Australian definition).
To re-iterate: CFS has the highest rate of increase in medical insurance claims over the five years (1989-1993) of any illness.

Proposed Pathophsyiologic Mechamisms of Chronic Fatigue Syndrome

"We must turn to nature itself, to the observations of the body in health and disease, to learn the truth" (Hippocrates c.460 BC)

Chronic fatigue syndrome represents a chronic, debilitating and prolonged illness characterised by numerous symptoms but most especially fatigue, cognitive dysfunction and pain.

Frequent but subtle physical findings support laboratory evidence involving excessive alpha-interferon production and functional brain scan evidence of central nervous system injury which is likely to be metabolic and may possibly be due to interferon itself.

Immune activation with excess lymph production may produce peripheral pain in certain tissues, which is then amplified centrally by injury to key central nervous system structures and is mediated by opioid receptor- linked alpha-interferon-induced neurotoxicity.

Fatigue itself may have cellular basis at a level of mitochondrial dysfunction.

Organ systems may be differentially affected and within organ systems there may be a mosaic of affected and unaffected cells, the sum of which defines the degree of organ dysfunction.

Immune activation and its effects on the CNS may set up a vicious cycle which is independent of an initial triggering agent or event (which may no longer be present).

It is also possible that a persistent causative agent(s) exists and plays an active role in the maintenance of this pathophysiology. The exact nature of this putative agent

remains unknown, but the clinical presentation and the presence of high levels of alpha-interferon or its subcellular effects favours a viral aetiology.

The Diagnosis of Chronic Fatigue Syndrome: an over-view of useful methods in general and specialist practice

"When a lot of remedies are suggested for a disease,
That means it can't be cured" (Anton Chekhov, 1860).

The diagnosis of CFS is made on clinical grounds. Post-exertional relapses, balance disorder, alcohol intolerance, pressure-like headaches and unrefreshing sleep add more weight to the clinical impression.

Essentially normal routine blood results which nevertheless yield some clues to this disorder help to confirm it.

There are many other tests which help confirm the view of CFS as a disorder of an immune activation state with neuroendocrine sequelae and with a variety of metabolic problems centred on the mitochondria.

Various functional tests of the liver, gut, autonomic nervous system and aerobic exercise potential can confirm impairments.

CFS is not unique on the issue of tests which support the diagnosis but do not categorically diagnose it: the diagnoses of multiple sclerosis, lupus erythematosus and mononucleosis are often supported by non-diagnostic tests.

Useful diagnostic procedures concentrate particularly on routine blood work. Just as there are a lot of interesting, observable but subtle abnormalities on physical examination, there are also subtle abnormalities on routine tests.

Immunological Tests

There are a range of useful tests, and a lot more attention to certain immunologic tests which look for a pattern of immune activation combined with discrete defects is helpful, ie. look for this pattern of immune activation and discrete immunological defects.

- low level ANAs (antinuclear antibodies) which fluctuate from positive to negative at low levels are very common
- various dysgammaglobulinaemias, including both high and low IgG levels with subclass deficiencies, are fairly common
- CICs (circulating immune complexes) can be common: immune complexes using ClQ binding assays are elevated in 35% of CFS patients against 2% of controls

- two-colour flow cytometry looking at various immune activation markers should be used --- the one which is most sensitive is the CD3 CD26 marker for immune activation. A very interesting one is the CD4:CD8 ratio, which can be extraordinarily elevated due to both CD8 depletion and CD4 expansion. This has been seen in a subclass of patients
- the Multitest CMI skin test has been useful as a simple, cheap, functional assessment tool: a hypoergic or anergic result should be interpreted as evidence of immune activation
- serum and then cell associated alpha-interferon levels show 60% positivity on serum and 90% positivity on cell associated testing
- IL2 (interleukin 2) receptor tests are very simple and can mark immune activation in the various immune function tests with respect to NK (natural killer cell) function. It is important to asses the NK killing per NK cell and not just the gross kill.
- various mitogen stimulation tests should be performed

The link between immune activation and CNS injury may be in the intense activation of alpha-interferon induced 2-5A antiviral pathway seen in the great majority of CFS patients --- alpha-interferon is known to induce neurotoxic injury to limbic structures and serotonergic pathways via opioid receptors agonist / antagonist.

Viral activity or re-activation tests

This area can be a swamp at times, but there are some interesting things becoming apparent in terms of antigen capture assays, particularly for HHV-6; this might be appropriate to identify a subgroup which really does have significant viral replication.

Metabolic testing

DHEA testing seems to identify a subgroup which does not do well over time.

Tertiary hypothyroidism (T4/TSH) should be monitored, as both of these are low and go down together in some patients with CFS.

Urinary free cortisol needs to be checked --- significant reductions in cortisol production have been seen in the seriously ill patient, sometimes requiring intervention.

One increasingly useful test is the urinary organic acid analysis as a fingerprint of metabolism.

Other useful tests

- liver function assays

- lactulose / manitol gut permeability assays
- serum lipid peroxides
- essential fatty acid analysis --- this has been useful in assessing primarily red cell membranes and in deciding whether to give the patient omega 6 or omega 3

Neurological issues

lumbar puncture and EEGs are not applied across the board but are useful for very ill individuals

Function Tests

Exercise ergometry gas analysis has easily been the most useful single test for arguing for disability in these patients; it is a measure of physical functioning and is well accepted by Social Security in the United States.

Cognitive evoked computer EEG may be very useful in establishing disability.

Tilt table testing establishes a dysautonomia.

SPECT scanning needs to be done with an MCUI type of analysis rather than just looking for asymetric hypoperfusion.

Routine tests in the Chemical Panel

LDH is low in a lot of patients. Of all the liver injury tests, this one may be most associated with function.

Uric acid and total cholesterol / HDL ratios can be clues to oxidant stress. In the seriously ill patient, uric acids go down under severe oxidant stress and HDL tends to go down as well.

Alkaline phosphatase may be elevated in these patients.

Complete Blood Count (CBC)

This can show an atypical lymphocytosis.

There can also be a leucopenia / leucocytosis.

In about 40% of CFS patients, the ESR is low. Women have a higher sedimentation rate than men, and the normal range shifts with age: older women have the highest sedimentation rate, so if a woman in her 30s has an ESR of 0 -3, it is actually outside the normal range.

From the above, a simple chemistry panel, immune complexes, immunoglobulin G, quantitated immunoglobulins and ANAs can display clues to the presence of CFS, the interpretation of which is of an immune activation state.

Management of CFS

The traditional treatment of CFS has been largely symptomatic and driven by anecdote. The problem with symptomatic treatment is that what may make patients *feel* better may not *be* better (such as suppressing cough in pneumonia or steroid therapy in AIDS). In CFS, treating the disease symptomatically seems to backfire in the sicker patients.

There is no best way to treat CFS patients.

The most important foundation in treating CFS is three-fold:

(1) Lifestyle adjustment
(2) Diet prescription
(3) Exercise prescription

A broad-based, comprehensive approach seems to work best and elements should include

- nutritional support such as diet adjustment --- a modified elimination and/or rotation diet, with polyphasic digestive enzymes with particular emphasis on proteolytic as opposed to lipolytic enzymes. The modified elimination diet eliminates gluten. Foods to which patients are sensitive or allergic should obviously be restricted

- supplements – broad spectrum multivitamin orally, with broad spectrum antioxidant orally (it may be dangerous to treat with high doses of antioxidant without attention to the recycler), high dose B12 (not because the patient is deficient in B12 but because they are deficient in an enzyme to which B12 is a co-enzyme), magnesium glycinate (which has excellent bio-availability with very few side-effects) and flaxseed oil (which has omega 3, omega 6 and omega 9 integrated in it -- this is really important in the subset of sicker patients). Magnesium and anti-oxidants protect the central nervous system against the potentially neurotoxic effects of certain compounds and for this reason are useful in overall management

- functional resuscitation therapies, especially for liver and gut function --- specially configured nutritional supplementation is necessary. There seems to be a problem in transporting food across the mitochondrial membrane and a defect in acylcarnitine (which is important not only in transporting fat, but in transporting toxins out of the mitochondria) can create problems in terms of energy generation

but can also result in poisoning of the mitochondria. CFS patients have nutritional utilisation blocks, mitochondrial transport blocks and cell homeostasis problems

- immuno-modulation

- assessment for treatable hormonal and neuro-endocrine issues

- pain management: the most important symptoms to address are sleep disturbance and pain: the approach to pain relief in certain very ill patients can easily be the most challenging problem in CFS management

- consideration of anti-viral agents in a subset of CFS patients

- activity limitation and modulation are very important, with limited exercise prescription. This includes pacing, the avoidance of over-heating, and no hot baths (as in multiple sclerosis). With a mitochondrial problem, aerobic exercise is a problem --- if patients exceed aerobic boundaries, they will get sick and relapse, so the limit must be defined by the patient

- hydrotherapy (used as an immune modulator as an issue of balance between immune suppression and activation). Some patients get worse with hydrotherapy --- the subset with low interleukin receptors tend to improve, whereas those with high IL2 receptors tend to get worse

- carefully selected drug therapy ---

  melatonin may be useful for sleep (in the study analysing cerebrospinal fluid of CFS patients, the third most common finding was melatonin deficiency of the central nervous system in the cerebrospinal fluid).

  DHEA showed mixed results.

- the single most important therapy should be to address the neurotoxicity present in these patients such as blocking NMDA receptor mediated amplification of non-specific brain injury. In brain injury of almost any kind, excitation of the NMDA receptor amplifies the original injury and if sufficiently amplified, will kill the cell; this receptor can be inhibited with magnesium, Klonopin, and possibly with other drugs which change the balance between NMDA and GABA firing --- under conditions of brain injury of whatever kind, NMDA fires in excess over GABA which has the effect of lowering the threshold potential, so neurons tend to fire inappropriately, scrambling information. If NMDA is in even greater excess, neurons fire all the time. Going the other way, GABA firing over NMDA increases the threshold

potential; if GABA continues to rise, the neurons shut down and do not fire at all. By using Klonopin and magnesium, the aim is to re-set the firing ratio so that information is processed better.

"Health is a state of complete physical, mental and social well-being, and not merely the absence of disease". (World Health Organisation, 1946).