The JOURNAL of IiME

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www.investinme.org

IiME Conference DVDs

These Invest in ME conference DVDs are professionally filmed and authored DVD sets consisting of four discs in Dolby stereo and in PAL (European) or NTSC (USA/Canada) format. They contain all of the presentations from Invest in ME International ME/CFS Conferences (2006 – 2012). Also included in the DVD sets are interviews with ME presenters, news stories and round-table discussions. These Invest in ME conference DVDs have been sold in over 20 countries and are available as an educational tool – useful for healthcare staff, researchers, scientists, educational specialists, media, ME support groups and people with ME and their carers/parents. Full details can be found at - http://www.investinme.org/InfoCentre%20Education%20Homepage.htm or via emailing Invest in ME at info@investinme.org

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Welcome to the Conference

Invest in ME welcome you to the 7th International ME/CFS Conference in London.

Invest in ME is a UK charity established in 2006 by ME patients and parents of children with ME (myalgic encephalomyelitis). The aim of the charity is to raise the profile of ME and awareness of the need for a strategy of biomedical research in order to treat and cure this disease. We hope to achieve this by educating healthcare professionals and the wider public about the true nature of ME. The conferences have formed a crucial part of this education. We recognise that the term CFS is used widely in many countries and the medical and research literature but we use the term ME and by that we refer to the WHO ICD10 classification G93.3.

We have come a long way since we started these conferences in 2006. The first few years involved more politics than science. This year we are pleased to be able to show interest from the wider academic scientific disciplines. The trend started with the publication of XMRV and ME/CFS by Lombardi et al. in the Science magazine in 2009. This led to controversies but brought ME into the attention of new researchers not normally involved in ME. At this time we await results from the NIH funded study led by Professor Ian Lipkin from Columbia University in USA to confirm whether a gammaretrovirus is found in blinded blood samples.

We are pleased to see that the interest in ME continues following on from the positive results of the Norwegian clinical phase II trials using Rituximab to treat ME/CFS patients. Last year we had the privilege of hearing pre-publication results from the principal investigators Professor Mella and Dr Fluge and we welcome them again this year to update us on their continuing research. The publication of this phase II clinical trial in Plos One in October 2011 led to much publicity in Norway. The Norwegian government apologised for the past treatment of ME patients which promoted ME as a behavioural illness to be treated with CBT (Cognitive Behavioural Therapy) and GET (Graded Exercise Therapy) despite patients having protested that such treatment made them worse.

Prior to the 2011 conference IiME organised a researchers meeting – our "Corridor Conference"

– where we hoped to use the opportunity presented by the conference to network and exchange information to launch new collaborations.
When one reads this Journal news will have been publicised regarding a two day closed researcher meeting which preceded this year's conference and which focussed on exploring autoimmunity and ME based on the results of the Norwegian Rituximab research. The Clinical Autoimmunity Working Group (CAWG) has been formed by the best of the best in the field of immunology/autoimmunity. The CAWG has been convened by The Alison Hunter Memorial Foundation and Invest in ME, in collaboration with Bond University, Australia and the University of East Anglia, UK. Dr Don Staines will be presenting a summary of this meeting at the 7th Invest in ME conference.
Invest in ME's intention is to fund research where we can and to facilitate cooperation and collaboration between researchers across the world. It is, we believe, only by these means that patients will be able to see real and rapid progress being made in treating this disease.
Patient power is described in the Journal with the Let's Do It for ME campaign being the best example of positive campaigning – where patients influence the progress of research.

The conference programme is a mixture of experienced ME researchers and clinicians such as Drs Peterson, Baraniuk, Marshall-Gradisnik, Staines, Kogelnik and recent newcomer to ME research, Professor Ljungar as well as experts in related fields such as Dr Delgado, Professor Fitzgerald and Professor Perry whose work is very important in helping us find clues to ME.
Professor Perry is also the recently appointed chair of the MRC Neurosciences and Mental Health Board (NMHB) so we welcome his input.
Then of course we all want to hear the latest from Dr Fluge's and Professor Mella's research.

Dr Ian Gibson, is a former cancer researcher and Dean of Biological Sciences at UEA and MP, will be chairing this year's conference.

Dr Gibson has been instrumental in helping Invest in ME initiate negotiations to set up an examination and research facility in Norwich using the excellent resources the Norwich Research Park has on offer.

The conference is focal point for research and networking but there is a great deal of work behind the scenes.

The Journal has a Scandinavian slant to it in this issue. This reflects our view and the events of the past year, that change will likely come from that direction.
Thanks to years of gallant efforts from the Norwegian ME Association, and now from the Norwegian researchers in Bergen, there is real hope of a breakthrough.
The Norwegian minister of health has officially and publicly apologised for the treatment given to ME patients.
The Swedes are similarly playing a forceful and proactive role in getting Swedish researchers and clinicians to the conference this year with EMEA Sweden member RME working closely with IiME.

We have articles from Norwegian journalist Jørgen Jelstad and Professor Olof Zachrisson from Sweden. Jørgen's article covers the story of the Norwegian researchers' work with Rituximab. Jorgen has written an excellent book "De Bortgjemte" – (The Hidden ones).
Professor Zachrisson's article covers experiences with staphylococcus vaccine treatment which was successful in alleviating symptoms but which is no longer available due to the vaccine manufacturers having taking it out of production.

While the charity attempts to initiate the first biomedical research into ME in Norwich as a prelude to further examination and research so we look to Scandinavia to lead the way in Europe.

Margaret Williams is a prolific and incisive commentator on the state of ME. She has produced another enormous piece of work on immunology – the theme behind this year's conference – and we are pleased to publish this in the Journal.
The Journal of IiME was created as a means of providing a broad spectrum of information on ME, combining biomedical research, information, news, views, stories and other articles relating to myalgic encephalomyelitis .

Invest in ME was set up with the objectives of making a change in how ME is perceived and treated in the press, by health departments and by healthcare professionals. We aim to do this by

identifying the three key areas to concentrate our efforts on in order to raise funding for biomedical research - education, publicising and lobbying. This will provide the focus and funding to allow biomedical research to be carried out.

Our aim is to bring together like-minded individuals and groups to campaign for research and funding to establish an understanding of the aetiology, pathogenesis and epidemiology of ME. We hope this will lead to the development of a universal diagnostic test that can confirm the presence of ME and, subsequently, medical treatments to cure or alleviate the effects of the illness

We believe that governments should provide a national strategy of biomedical research into ME to produce treatments and cures for this illness.

Since our last conference Invest in ME has been working to initiate an examination and research institute in Norfolk, UK, which would properly diagnose and then research people with ME. The proposal is available here and is described later in the Journal. Thanks to the efforts of the IiME steering group, which includes Dr Ian Gibson who has been working tirelessly to support this proposal, we have come within one decision of initiating this proposal and creating a unique UK scenario which would have the potential to lead the world.
But vision is meaningless without action and we have to continue to debate, discuss and promote this work to enable others to see the possibilities.

The unique blend of biomedical research, objective data presented by our distinguished speakers is testament to the increasing knowledge regarding myalgic encephalomyelitis. To repeat a line from a previous Journal, which is still relevant today - if a sea change in the perception of ME is occurring then it will be based on the good science and objective data (represented by our conference speakers), effective advocacy (represented by conference delegates from twenty different countries and from ME support organisations such as EMEA and AHMF working together across the world).

Change will be forced by patients – the alternative in doing nothing is not an option.

Building a Future for Research into ME

The Corridor Conference organised in London last year by IiME and the more impressive and forward-thinking CAWG research group which meets in London this year before the conference is our way of making progress in biomedical research into ME. We attract experts from other disciplines to bring their expertise and skills to bear on this disease. By doing this we can bypass the negativity and misinformation which has pervaded the perception of ME for a generation and instead focus on proper science.

The Let's Do It for ME campaign and our core group of supporters are helping to fashion a change in ME research and this is determination and enthusiasm will influence researchers – both within the ME research area and those from outside.
The Invest in ME conferences bring together this optimism and determination in a happy mixture of wanting, needing to learn, optimism and hope that things will improve. At the conference there will be researchers, clinicians, nurses, patient groups and patients, advocates and, we always hope, a sprinkling of as many politicians, journalists and others whom Invest in ME self-fund to allow people to be exposed to real science.
We would like to thank our friends at the Irish ME Trust for once again sponsoring one of the speakers at the conference.

The IiME conference is not only a platform for proper, high-quality science – we hope it continues to be a platform for the hopes of millions of people around the world.

Enjoy the Journal. Enjoy the conference. Let's do it for ME.

Let's do it for ME!
Supporting Biomedical Research into ME
www.investinme.org
Registered Charity Number 1114035

In the summer of 2011 ME patients and their families were exposed to a torrent of inflammatory and biased media mis-information in a seemingly coordinated campaign relating to the illness, to patients and to research into ME. Misinformation and ignorance about ME is not a new response from a simplistic and manipulated press.

The distress and concern caused to Invest in ME supporters and their carers forced the charity to submit a formal complaint to the Press Complaints Committee about these series of articles [1] – all seemingly emanating from the same source. The charity's actions were not due simply to the fact that extremist views of the disease and the alleged actions of patients were being falsely portrayed by the media and by paid buffoons masquerading as journalists – it was due to the effect it had on patients who yet again were seeing their situation, and the disease from which they are suffering daily, being ridiculed and misrepresented by poor journalism and missing editorial rigour.

How does a patient community respond to such prejudice and propaganda? How can a change be made in the way that the media view this disease and the sick and vulnerable people that suffer from it?

At around this time an idea was born by Jo Best and helped on by Jan Laverick and Paul Kayes – all ME patients. Instead of continually reacting to what others were doing or saying they decided to take a proactive approach. A campaign was started to support the Norwich examination and research facility proposal which Invest in ME had made to initiate a UK Centre of Excellence for ME.

The difference with this campaign? To use the skills and ideas of patients who want more than anything else to regain their health. By harnessing these ideas and enabling people to feel positive about doing something themselves to effect change then the campaign could be turned into something which was fun. Positive campaigning – with an objective to fund sorely needed translational biomedical research into ME and to harness patient power to influence ME research – something which has been missing from the equation.

There are an estimated 250 000 ME patients in the UK, twice as many as MS patients and MS charities manage to raise millions of pounds for research. ME patients and their families should be able to do the same.

The Let's Do It For ME campaign is a positive and proactive campaign. The aim is to raise funds for biomedical research but everyone's input is welcomed - be it just ideas or moral support for other people's fundraising.

Supporting Invest in ME Charity No. 1114035
Let's do it for ME!
Myalgic Encephalomyelitis
ldifme.org

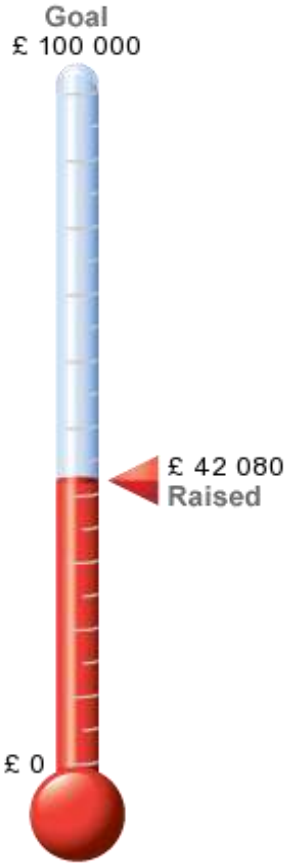
Whilst raising funds for biomedical research the campaign is also raising much needed awareness and allowing correct information about ME to be disseminated.

Carole Carrick and her husband Clive have been doing several supermarket collections and by doing so they have met many members of the public and passed on information about ME by talking to people. Carole also attended an ME event at the Scottish Parliament in Edinburgh as an IiME representative and again raised much needed awareness of IiME's activities and the LDIFME campaign. Kathryn Lloyd was so severely affected for many years that she could not even

speak so she raised several thousand pounds by doing a sponsored silence. James Wythe pledged to raise £3000 if others raised a matching sum. It was achieved. The fundraising efforts have grown and now we have several people taking part in various events.

There are marathon runners – in Brighton, Paris and Edinburgh. Little 10 year old Teigan ran a mini-marathon to raise funds for IiME. Teigan's mother suffers from ME . There are people taking part in events such as 'The Big Sleep', school non uniform and awareness raising days, art exhibitions etc. Jan Laverick and Carmel Hillary have set up online shops to sell t-shirts and other gifts with IiME and LDIFME logos.

In order to facilitate fund-raising campaigns a subscription to Just Giving has been set up thanks to a kind donation to cover the first year's subscription fees to Just Giving.



In a short article such as this we cannot mention everyone who has taken part, or contributed with money or ideas. But the campaign has been effective and re-energised research, making the go-ahead for the IiME proposal nearer to reality.

Rather than waiting for others to do things – a strategy which has not faired well over a generation – the people involved in the efforts to make the IiME proposal a reality are taking it on themselves to make a difference.

Let's do it for ME! is a patient-driven campaign to raise awareness and vital funds for a centre of excellence for translational biomedical ME research, clinical assessment, diagnosis and treatment for patients, and training and information for healthcare staff based at the University of East Anglia in the UK and aiming to work collaboratively with international biomedical researchers.

Reference:
[1] http://www.investinme.org/Article-505%20PCC%20Complaint%20Aug%202011.htm

(The pictures in the mosaic on this page are some of the volunteers and supporters from the Let's Do It for ME campaigns).

Further details –
http://www.investinme.org/IiME%20Awareness%20Events%20LDIFME.htm
or
http://blog.ldifme.org/

ME FACTS

1969: the World Health Organisation classified ME as a neurological disorder.

DIAGNOSTIC CRITERIA
The New International Consensus Criteria for ME - content and context
by Professor Bruce M.Carruthers, MD,CM, FRCP(C)

The New International Consensus Criteria for M.E. - content and context

By Bruce M.Carruthers, MD,CM, FRCP(C).

CONTENTS

Sir William Osler said "Look wise, say nothing and grunt. Speech was given to conceal thought." This is a typically Canadian form of advice. As a compatriot, it is with great trepidation that I deviate from it.

In the new ICC the general thrust of the 2003 Canadian Consensus Criteria is retained but developed further.

- We recognize the international scope of the problem of ME and its solution by moving to an international consensus panel.
- The 6 month waiting period is no longer required, but left to clinical judgment.
- The distinct dynamical symptom pattern of Post-Exertional-Neuroimmune-Exhaustion is kept criterial and further articulated as having the dynamical structure of unusual physical and/or cognitive fatiguability after the appropriate kind of exertion, which may be immediate or delayed, and has a prolonged recovery period.
- Other symptoms and signs arising from dysfunction within the following subsystems often share a coherent dynamics with PENE, to suggest an interactive underlying causal context- neurological (neuro-cognitive, pain processing, sleep disturbances, neuro-sensory and motor), immune, gastrointestinal, genitourinary and endocrine subsystems, as well as dysfunction in the energy production and transport systems-cardiovascular, micro-vascular, respiratory, and maintenance of thermostatic homeostasis and intolerance of temperature extremes).
- Interactive dynamical pattern matches between the criterial PENE symptom pattern and the symptom/sign patterns arising from other patho-physiological subsystems are first articulated in individual patients and then as projectable in individuals, if they remain coherent and consistent over time, as well as onto larger groups of similar patients. Thus these observations become mutually confirmable as pointing to real and natural structures/patterns/kinds that exist "out there" as part of the causal structure of the body in its world- and not as creatures of the mind that happens to be trying to observe and re-present it (nominalist, constructed kinds).
- Modulations for paediatric cases are added.
- Exclusions that are likely to become necessary for the individual case as part of her/his differential diagnosis are listed.
- The ICC keeps its focus on selecting relatively homogeneous subsets of patients with interactive symptoms, essential for clinical research if its observations are to be properly controlled, while including a discussion of recent pertinent research results.

Context

"ME" as the name for a chronic fatiguing disease of bio-pathological causation has a long history, primarily in the U.K., even though the specific bio-hypotheses of causation underlying its name proved difficult to confirm, given the technology available at that time (1954-94). Over vigorous objections, the name then largely shifted to "CFS", a noncommittal umbrella disease concept that includes all fatigues that are severe, chronic and unexplained, but ignores the "syndromeness" embedded in its etymology by putting symptoms onto lists that ignore their dynamical relations of causal inter-activity. This latter points to a common underlying causal structure, however complex and currently unknown, and is found in the etymology of the word "syndrome" (Gk. running together). However elaborately symptoms are entered into lists, the problems resulting from this neglect of their natural inter-active dynamical causal structure will remain.

- In his study of the Reeves criteria for Chronic Fatigue Syndrome, Jason et al found that only 10% of patients identified as having CFS actually had ME, and confirmed the efficacy of the Canadian criteria in separating out this 10% subset.(J Disabil Pol Studies 2009; 20: 91-100).

- Why was this maneuver of the Canadian criteria so effective in separating out this subgroup? By recognizing that fatigue showing the specific dynamical patterns of ME characterized a large subset of fatigued patients, and thus was different in kind from the patterns underlying the majority of severe, chronic and unexplained fatigues (CFS). It thus pointed to a different underlying causality- a natural kind or real pattern whose underlying causal organization lies in the world, not just our representative models of the world, that could be researched using biological methods- given adequate comparative controls.

- With major advances in technology, recent research guided by properly scientific hypotheses has given strong support to "ME"s implication that a different underlying causal structure- one involving inflammation and dysfunction within the CNS, ANS and immune systems, plus more- underlies this large subset of CFS patients.

- While it has always been essential, it has now also become urgent to segregate the subset that we are calling ME more clearly, using the ME International Consensus Criteria, so that researchers can confirm/disconfirm their results using patients who have chronic fatigue of this clearly bio-pathological origin. Otherwise the all-inclusive umbrella of "CFS", in ambiguating natural and psychosocial kinds of fatigue, will continue to dilute the results of any investigations and maintain the pervasive confusion resulting when biopathological kinds are mixed indiscriminately.

Conclusion

- The results of Jason et al's studies have confirmed that the Canadian Definition of ME/CFS had clearly separated cases who have ME (fatigue of bio-pathological or natural origin, arising out of a pathological causal structure present in the world apart from the mind that is observing it) from those who have CFS (which includes the minority of the specific natural kinds we are calling ME plus a majority of fatigue kinds that are secondary to other diseases, plus parts of the normal homeostatic activity-rest cycle designed by evolution, plus fatigue kinds constructed by the re-presentational observing/thinking and thus dualistic model-making mind).

- The prevalent use of symptom-based definitions has been adding to the confusion by analyzing complex syndromes using a Cartesian method of analysis that isolates symptoms by putting them onto standardized lists of separated subjective entities, thereby bypassing the dynamical subjective/objective interactive processual causal on-line context that points to an underlying interactive causal

organization, even if we are as yet unaware of its details.

- Contrariwise the new ICC encourages that symptom structure be observed on-line as interacting embodied and embedded causally interactive dynamical process(es) that have multiple subjective/objective manifestations. These are first observed (or ignored) in a clinical dialogue as (subjective) symptoms and (objective) confirmatory signs which are disambiguated on-line, in their natural context, as temporally dense and as having felt/observed causal efficacy. These individuated observations are in turn confirmed by objective biochemical measures, pathophysiological functional testing and imaging. The "same" phenomena can also be studied off-line using epidemiological studies which observe the generalisable constancies found in groups of variously homogenous groups of cases using standardizing techniques of questioning and observation to obtain generalisable results and case definitions. In the standardized and properly randomized environments of scientific experiments, the effects of interventions can be properly controlled, and thus general rules of causality inferred and quantified.

- As the ICC panel members add clinical guidelines and symptom scales (ICSS), these three essential kinds of observation will be integrated by using a transductive and mutually confirmative language that matches the dynamical causal patterns to be found in each realm. This pattern "language" must be flexible enough to negotiate the changes in scale and context involved in comparing observations arising from disparate clinical, epidemiological and research methodologies, scales and contexts, all of which necessarily remaining distinct, yet interrelated. We are confident that this will lead to mutually confirmed outcomes that can be generalized and standardized world-wide- meanwhile remaining adequate to the particularities and demands of each patient's complex illness/disease structure.

- As Osler also said "Listen to your patients. They are giving you the diagnosis". Now we have the technology to confirm this directly for this complex disease- if we use it.

Since this presentation was given in Ottawa Sept 24, 2011, the Journal of Internal Medicine has published 3 articles concerning these issues that are freely accessible on line-

1/ The ICC for ME was published- J Internal Med Oct 2011, 270: 327-38.

2/ A critique- ´A controversial consensus" published JWM van der Meer and AR Lloyd J Internal Medicine 271: 29-31, Jan 2012. In particular the above authors discussed the "unscientific" way the ICC was laid out, discussing the "pseudoscience of pathophysiology" "notional" pathophysiology, and the "intrinsic heterogeneity in syndromal diagnoses" but neglecting to mention how their recommended approaches to syndrome description had contributed to this situation by treating symptoms as separated subjective things on lists, thereby destroying any consideration of their embodied interactive dynamic context or "syndromalness" (Gk etymology, running together on a track), and rendering research directed towards underlying causality more elusive.

3/ A rebuttal of the critique by G Broderick J Internal Med vol 213-17 Feb 2012. corrects some of these misapprehensions, and points out that the Reeves and Oxford criteria for CFS select patient sets that are approximately 10x larger and more inclusive than those selected by the Fukuda criteria, and that the Canadian consensus criteria selected patients with even more severe physical functional impairment, less psychiatric comorbidity than the Fukuda definition(see Jason et al Am J Biochemistry and Biotechnology 6: 120-135, 2010) and obviously brought to salience the distinctive pathophysiological pattern of delayed reactive fatigue, which it made criterial. This symptom is not the simple name of an isolated subjective feeling put on a list, but points to its participation in a higher level fatigue/activity

control network which we know to be present by its disregulated causal efficacy in the world, even if we do not yet know what its details are, and which we are calling "ME" in honor of the earlier (and current) sufferers and prescient observers of this kind of suffering. Other earlier and revised case definitions based on the disease concepts of Ramsay had made postexertional malaise and impairment of memory and concentration central to the diagnosis of ME (Lloyd AR et al Med J Aus., 153: 522-528, Goutsmit, E et al Health Psycholog. Update 18:27-31), but none before the Canadian Definition of 2003 had made this specific dynamic and projectable pattern of pathological fatigue criterial for the diagnosis of ME/CFS, and the ICC case definition of ME is carrying on and developing this strategy further. The specificity of this illness pattern provides a level of detail that is necessary for patients to adapt to the aberrant pattern of fatigue as experienced in their own illness using pacing. Research can be designed to study the pathogenetic details of this particular pattern and the many others that I expect will be uncovered as the ICC strategy is used more widely, with the assurance that results are not being continually diluted out by the 90% majority of CFSers who don't have this kind of fatigue pattern. We can finally search for specifically directed remedies. This is the way towards scientific progress after what has been a long delay, indeed a paradigm war- not arguments between results but between opposing assumptions made before beginning observations.

All three of these contributions agree on one point- that whatever it is we are talking about, it is a complex disease/illness- but on little if nothing else. There was special confusion on whether we were talking about CFS or ME, regarding them as mutually exclusive dualistic entities and not complementary parts of a single disease concept. And confusion reigns about what we mean by complexity itself in various realms (the topic itself is complex)- and we are dealing with the realm of medicine, where not much serious thought has been put to it as yet, e.g. producing long symptom lists and symptom counts doesn't help.

Simple or Complicated structures have a known stable causal structure, of variable intricacy, that hence are predictable if you can extrapolate from knowledge garnered from one astute observation. Complex structures do not, as their causal structure is forever recursively changing as a result of the causal interaction of their constituents-and hence are inherently unpredictable. As a consequence a complex structure must be observed continually, while the complicated one does not have to be, while confirming/disconfirming inferences, tests, and imagings are made. For complex diseases the only observer who is constantly observing the patient is the patient her/himself. We all must learn to utilize this kind of continual common sense self-observation by patients in dialogue with their physicians, as we together observe the development of complex diseases over real time through a robust and productive doctor/patient relationship. This will entail a large qualitative shift in attitude and appreciation of the value of the direct self-observation of illness structure as it evolves in real time, if done properly- and without diversion into cognitive dualisms.

There are also repercussions of post-cognitive theoretical moves in psychology into direct non-representational perception and radical embodied cognitive science (see "Radical Embedded Cognitive Science) Anthony Chemero MIT Press, 2009 and "The Mind, the Body and the World- Psychology after Cognitivism? Ed. B Wallace, A Ross, J Davies and T Anderson, Imprint-Academic.com, 2007.), which point to the need for a distinct shift in strategy (in our realm of medicine) from its current emphasis on developing generalized cognitive disease models to directly observed, individuated diagnosis of illness and its therapeutics. This is also emphasized by the development of bottom-up systems biology and translational and systems medicine (Nielsen J.J Internal Medicine 271, pp 108-110). Our current treatment of symptoms and syndromes in diagnosis and prognosis, and of pacing and the role of self-organization in therapeutics, will also need great adjustments as we move from an "anthropogenic" to a "biogenic" approach to them. (see "The biogenic approach to cognition" Pamela Lyon, Cognitive Processing 2007: 11-29) .

Opportunities are arising with the rapid development of technology to allow direct confirmation of the clinical symptoms and signs observed by individual patient/physicians without a detour through the medical model, but by attending to directly observed individual illness structure, with mutual transductive confirmation

of the symptom patterns felt directly by a patient in dynamically congruent patterns observed within the under-overlying causal systems at different OMIC scales (genomic, cellular, organ, physiological system, as well as at the emergent organismic, organismic/environmental/ epidemiological, etc. scales.

What is in process for our ICC endeavour are the preparation of an ME Physicians' Primer/Guidelines and the preparation and testing of an International Symptom Scale to improve cross-standardization of symptom questioning when comparing groups of patients where clinical epidemiological and other statistical studies are being planned.

ME FACTS

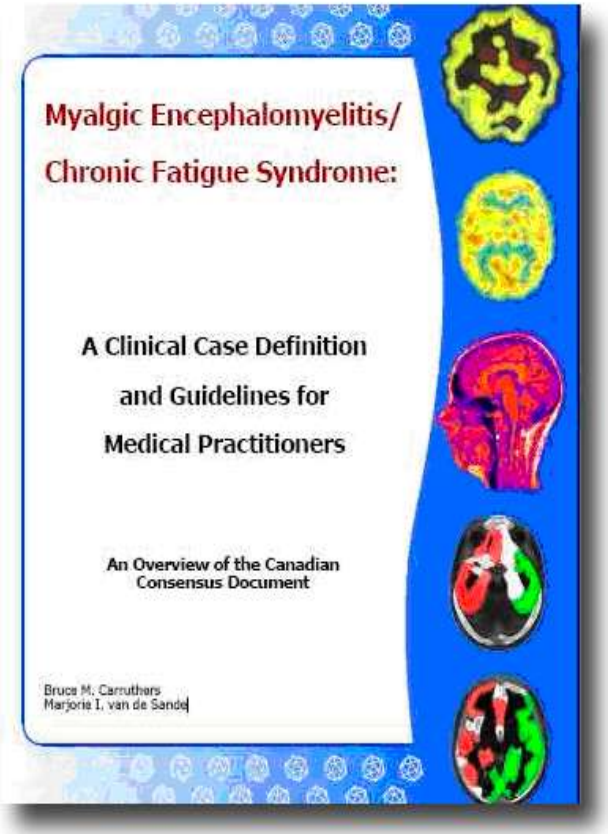
1978: The Royal Society of Medicine accepted ME as a nosological entity.

The Canadian Guidelines

Invest in ME are the UK distributors for the Canadian Guidelines. Described even by NICE as "*the most stringent*" guidelines available these are proper, up-to-date clinical guidelines which can also be used as a base for research criteria.

Findings from the study by Leonard A. Jason PhD (Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome) indicated that the Canadian criteria captured many of the cardiopulmonary and neurological abnormalities, which were not currently assessed by the Fukuda criteria. The Canadian criteria also selected cases with *'less psychiatric co-morbidity, more physical functional impairment, and more fatigue/weakness, neuropsychiatric, and neurological symptoms*' and individuals selected by these criteria were significantly different from psychiatric controls with CFS. The Canadian Guidelines provide a means for clearly diagnosing ME and were developed specifically for that purpose.

They are an internationally accepted set of guidelines for which many in the ME community have been campaigning to be adopted as the standard set of guidelines for diagnosing ME.



ME STORY

"I have since been sent to another neurologist after my doctor found I was Rhomberg's positive, who made me walk, did a scratch test on my feet, checked the weakness in my legs, and said quite rudely,

"***you have ME, I am not going to waste time doing tests on you***"

and that was it.

I walked away feeling like I had wasted this man's time. I pray one day a cure will come our way." - Rowan

- *"Personal Stories of ME Sufferers - http://www.investinme.org/mestorygallery1.htm*

THE DRUG AND THE POSSIBILITY OF CHANGING EVERYTHING

Author: Jørgen Jelstad

Jørgen Jelstad is a Norwegian journalist and author of the documentary book "The Hidden Ones: and how ME came to be the most controversial disease of our time" (only available in Norwegian – named "De Bortgjemte"). The book received great reviews from Norwegian critics, some of them citing it as a must-read for health care workers. It has also been referenced on several occasions by some of Norway's most prominent politicians. Jelstad has a blog: www.debortgjemte.com

This article will focus on the recent Rituximab findings in ME/CFS, something Jelstad has followed closely since he started working on the book in 2009.

"They soon found that new ideas aren't always welcome in science – even if the old ones aren't working."

- Switch off, switch on, The National, 2009.

2004: Patient zero

Anne Katrine walks into the Cancer Department at Haukeland University Hospital in Bergen in 2004 to get treatment against the lymphoma the doctors discovered one year earlier. After four rounds of chemotherapy the cancer seemed to be beaten, but suddenly it came back and she is in for her second treatment regimen.

Anne Katrine also has ME/CFS since she suddenly fell ill with mononucleosis in 1997. For several years she had mostly been housebound with muscle pain, problems with sleep and great cognitive difficulties. An overwhelming fatigue and malaise has made her unable to leave the house for more than short periods of time.

Five weeks after starting the new treatment against lymphoma, something unexpected happens. Suddenly she notices a marked improvement in all the ME/CFS symptoms that she has endured for more than seven years. She has never before experienced anything like this. Her teenage son had one time told her that he was not sure if he could manage to live with someone as sick as his mother. Now, they were able to go to Turkey together for the holidays.

But suddenly it all comes back. The headache, the aching muscles, the cognitive decline and the devastating fatigue and malaise. Back to scratch. "When you had cancer, mom, we had the best dinners ever," Anne Katrines daughter tells her after the relapse.
Sitting in his office at Haukeland University Hospital, cancer specialist Øystein Fluge scratches the back of his head, puzzled. What really happened to his patient Anne Katrine?

For years to come he cannot forget what he saw during these months in 2004.

2009: Pioneering

In October 2009 I sat in a small office at Haukeland University Hospital in Bergen, a city on the west coast of Norway. I remember it well. The two doctors enthusiastic telling of their surprising tale. I was in the very beginning of researching my book about ME/CFS when I came across a small pilot study from the very same people I was meeting for the first time this day.

Even then, without the extensive knowledge about ME/CFS that I have now, I remember thinking: If this turns out to be true, it will change everything.

It was a beautiful sunny day, with snow covering the peaks around Bergen. On my way to the meeting with Professor Olav Mella and Doctor Øystein Fluge, I saw signs pointing the public to the mass vaccinations against the swine flu. In a few weeks Norwegian authorities had spent more money on buying vaccines than everything the American government had spent on ME/CFS research for the last 25 years.

I remember seeing that as a telling comparison pointing towards a still grim future for ME/CFS. But now, I was wondering if these two doctors story could be a turning point. After 25 years of controversies, lack of funding, maltreatment, ridicule and dashed hopes. Could this be the game changer?

Dr Fluge was talking about Anne Katrines remarkable story of recovery from most of her ME/CFS symptoms, and after those months she had never let Fluge off the hook. She begged him to find out what had happened. And in the end, Fluge and Olav Mella, the head of the Cancer Department at the hospital, decides to give it a try even though they have never before worked with ME/CFS, barely heard of it.

“Our starting point was: Could this be an autoimmune disease? And if so, could it be that it was methotrexate in Anne Katrines treatment that was working on her ME/CFS symptoms”, said Fluge.

Methotrexate is a medication which dampens the immune response. It is used in large doses in some cancer treatments, but it is also used in smaller doses against different autoimmune diseases, for example rheumatoid arthritis. Anne Katrine had gone through three different courses of cancer treatment, but only with one of them did she experience a near resolution of her ME/CFS symptoms. In that treatment she got methotrexate, something she did not get during the other treatments.

“We could not know if this hypothesis was right, but our idea was to try to treat CFS with Rituximab, which is a medication that works directly on the B-cells in the immune system,” said Fluge.
Like methotrexate, Rituximab is a medication that dampens the immune response, but through a different mechanism. It basically wipes the B-cells out for a few months before they slowly grow back. Both of these medications are used in the treatment of cancer and autoimmune diseases. In 2007, Fluge and Mella decided to do a small pilot study on three ME/CFS patients. One of the three patients they contacted was Svein.

“Before Olav Mella called me, I remember I discussed with my wife how long I would manage to go on with this disease,” said Svein when I asked his story in a phone interview.

He worked at the local hospital, but after a serious viral infection ten years earlier he never recovered. For a long time he tried to stay at work, but in the end had to give it up.

“I have been so ill that I was bedridden and had to get help to get to the toilet. But of course, I still hope to get back to work some day,” Svein said.

Six weeks after his first infusion with Rituximab something happened. In just a few days Svein experienced major improvement in all ME/CFS symptoms.

“My father in law has a cabin, and it is situated just a hundred meters from the road from where we had to walk. Usually my stay at that cabin had been just managing to get there, and then I had to lie on the couch or the bed during the whole stay. Now I went skiing with my kids,” said Svein.

In their pilot study, published in BMC Neurology in early 2009, Mella and Fluge writes:

He could take one-hour walks and started to do carpentry on his house. Myalgic pain was markedly reduced. Cognitive functions improved remarkably, and he could now read a whole book without interruption. The hypersensitivity to noise decreased. He and his wife confirmed that family life had improved considerably.

“After my first treatment I finished two books in a weekend. Before treatment I could not even read two pages,” said Svein.

But after ten weeks of major improvement Svein crashed. Back to a life within the four walls of his house. All the symptoms came back as fast as they had gone away. He received a second treatment

course, and the same thing happened. Major improvement after six weeks, then ten weeks with maintained improvement, and then a crash.

In February 2009 he got a new infusion.

"Then I had the best effect so far, and it lasted even longer. I started doing carpentry on the house, made a new roof and new walls, put down cables. I throw myself at these kinds of projects when I feel better, because I feel there is so much I have undone. As soon as my body functions again, I'm ready," said Svein.

Before treatment with Rituximab, Svein had only been able to watch pictures of his kid's activities outside the house.

"That feels terrible. When I get this treatment I manage to participate. It is like being brought back to life again," said Svein.

The two other patients in the pilot study, one of them Anne Katrine, and the other a woman in her early twenties, had similar major improvements after Rituximab treatment. Mella and Fluge were themselves surprised when they saw the astounding pilot results, where the patients at times experienced near resolution of all of their symptoms.

"Then we felt that we were touching a central mechanism in the disease," said Fluge back in 2009.

They started a double blinded, placebo controlled and randomized study on Rituximab in 30 ME/CFS patients – what is called a RCT. Placebo controlled means that the patients are divided into two groups – 15 got placebo (salt water) and 15 got Rituximab. Double blinded means that neither the patients, nor the researchers, know who gets real drugs and who does not. Randomized means that it is random which group the 30 patients end up in. This is considered the gold standard in medical research on drugs.

At my first meeting with the two doctors that day in 2009 none of them knew if their study would turn out positive. They did not yet know which patients got the drug and who got placebo.

I followed Mella and Fluge closely the next two years. Ups and downs. Uncertainty and promise. And now we all know: new hope. Let us take a leap to October 2011.

2011: Praise

"It's the most encouraging drug result so far in the history of this disease. Although it's a small trial, it's produced dramatic results," said Charles Shepherd, MD and medical advisor to Britain's biggest patient association for ME/CFS, to New Scientist in October 2011.
The Norwegian Rituximab study had just been published in PLoS ONE, and it generated a massive amount of media coverage. "Immune system defect may cause ME" reported BBC. "Cancer drug can help chronic fatigue" was the headline in Europe's leading news magazine Der Spiegel.

Never before had a study on a drug in ME/CFS had such promising results.

The study on 30 patients showed that 10 out of 15 patients (67 %) got a significant improvement from the cancer drug Rituximab which wipes out most of the B-cells in the immune system. 9 out of the 10 responders got a "major improvement" according to the paper. In the placebo group only 2 out of 15 (13 %) got a significant improvement. The result was 10-2 between the groups. Or 9-1 if you only look at "major improvers". It turned out that most of the responders, unlike two out of three pilot patients who were early responders, started their improvement as late as 3-7 months after the infusion with the drug. Another significant finding was that most patients relapsed when the effect of the B-cell depletion wore off, which is consistent with the effect of such treatment in some autoimmune diseases. "Thus, we believe that B-cell depletion targets a central player in the pathogenesis of the CFS disease, directly or indirectly", the study authors wrote in their paper.

The director of Haukeland University hospital, Stener Kvinnsland, who was not directly involved in the study, said to the Norwegian broadcaster TV2 that he "had a strong feeling that this was a breakthrough". Dr. Kvinnsland is one of Norway's most respected cancer researchers with a solid track record, and to a Norwegian newspaper he said that the Rituximab finding was one of the

most exciting things he had followed in his professional career.

Professor Carmen Scheibenbogen, Deputy Director of the Institute of Medical Immunology at the Charité University Hospital in Berlin, described the results of the study as a possible breakthrough. “This is a very important first step. For the first time, a therapeutic study has been conducted with medication that was originally applied to the immune system, and which proved effective for a majority of the patients”, she told bto.no.

In Norway, a country where ME/CFS has generated a lot of media attention the last few years, the Rituximab study led to a media blitz. For several days the media reported on the study, the lack of good care for the patients and all the broken promises about better services for ME/CFS patients from the government and the responsible health care providers.

It was like Rituximab was a tipping point for not longer being able to give the impression that this disease was not real, or that it was mainly a psychosomatic problem. Because how do you argue against a big gun cancer drug? In a way, Rituximab did not just heal some of the study participants, it also healed the self-respect of thousands of Norwegian ME/CFS patients who finally experienced something else than suspicion and disbelief.

In a rare public statement the National Institutes of Health in Norway even apologized to the patients for the lack of services and years of mismanagement.

Before the Rituximab study hit the news, I called Sheba Medical Center in Tel Aviv to talk to the Israeli scientist and world renowned expert on autoimmunity, Yehuda Shoenfeld. He is editor in chief of Autoimmunity Reviews and has written several books and published hundreds of scientific articles on autoimmunity. In a review article in 2009 he wrote that recent findings in ME/CFS “points toward an ongoing autoimmune phenomenon in such patients that, although not fully understood, is likely to be enhanced by the presence of certain infectious agents and other adjuvants”.

“I cannot say for sure that this is an autoimmune disease, but CFS has a lot in common with this group of diseases”, a busy Shoenfeld told me over the phone.

At this time he had only seen Mella and Fluge's pilot study on three patients, but he said that what they reported there looks much the same as what you see when you use Rituximab in diseases like rheumatoid arthritis and SLE (lupus). Then he said that if they got positive results in a controlled study, it would indicate that a central mechanism in ME/CFS will be found in the immune system.

I asked him if that would be surprising to him. “No, not to me, but it depends who you ask. I have the idea that CFS belongs in this group of autoimmune patients”, said Shoenfeld.
I have since talked to several international ME/CFS experts, all of them enthusiastic about the Rituximab results. At last year’s Invest in ME conference I sat down with one of the most respected ME/CFS-clinicians, Daniel Peterson, and asked him his thoughts.
- I think it is a crucial step forward, he told me.
And then he went on to say that he had seen effects of Rituximab himself. Several of his ME/CFS patients had developed lymphoma and therefore got treated with Rituximab, one of them for several years.

- And after starting treatment his ME/CFS symptoms disappeared, said Peterson.

The future: Persistence

Of course, like everything in ME/CFS, no promising study without controversy. So the study in PLoS ONE also met criticism right away. This is science after all. Controversy is the rule, and more so in ME/CFS than anything else. A group of prominent ME/CFS researchers commented the study at the PLoS ONE pages, implying the results were oversold and with methodological flaws, and they challenged the conclusions. Then one of the world leading authorities on Rituximab quickly commented on a lot of flaws in the critics own criticism. Professor Jonathan Edwards from University College London said their criticism “contains several errors”, and went on to say that the “trial’s authors give the account that is by far the most consistent with the data”.

"In the end I think we have to find the cause behind the disease, or else no one will believe us. If we are right, which I think we are, we will make it. In a few years I think the scientific community will have the answer", said Fluge responding to some of the doubting critics.
It is important to acknowledge, like Fluge and Mella themselves have repeatedly said, that there is need for bigger studies before concluding on Rituximab and ME/CFS. And this study, like every innovative scientific study, also needs to be subject for criticism and disagreements to make headway for what we all want in the end – the truth. So why did I mention Jonathan Edwards? I did because he has been here, right where ME/CFS is now with Rituximab, just with a different disease. And Jonathan Edwards won the dispute. No one ridicules his ideas anymore.
In the 1990s Edwards, together with another British scientist, Geraldine Cambridge, came up with a theory about possible B-cell involvement in rheumatoid arthritis (RA). They met a cold shoulder from the rest of the research community. The importance of T-cells was then the only accepted theory in RA, and therefore most in the medical community automatically thought that the theory of Edwards and Cambridge were not worth pursuing.
But Edwards and his colleagues pursued their idea despite the resistance, starting off with a small pilot study on Rituximab in five RA patients.
"When the patients' B cells disappeared, so did most of their arthritis," Edwards told New Scientist in 2001. Three of the five patients remained well for a longer period, while symptoms of the disease came back in two patients once their B cells returned.
After years of unproductive battling trying to get this groundbreaking idea of the importance of B-cells in RA acknowledged in the medical community, Edwards talked to the press, and the story made headlines. Something which of course made some of his critics even more critical, but it worked. Finally they got funding for a big study on Rituximab in RA, and in 2004 the results were published in the prestigious New England Journal of Medicine. The result? Rituximab turned out to be a superior treatment in the study, and suddenly B-cells were on everybody's lips.

An article on the history of RA and Rituximab in The National in 2009 ends by mentioning Mella and Fluge's pilot study on Rituximab in three ME/CFS patients, which then had just been published:

"With so few patients, it's hardly definitive proof of a cure. Yet it is just the situation Prof Edwards and Dr Cambridge found themselves in a decade ago. CFS sufferers must be hoping medical researchers are not about to repeat history by rejecting these intriguing findings out of hand – despite not having any better ideas themselves."

Against the odds, Jonathan Edwards and his colleagues turned the whole field of RA around through pure persistence. He definitely knows that paradigm shifts do happen in medicine. No stranger from controversy, maybe Edwards gets that old feeling back reading the PLoS ONE study from Mella and Fluge, tempting him to have his say in public. Maybe he knows that the Norwegian scientists are in for a hell of a ride.
And maybe, just maybe, he wants them to win too.

After the article was written Jørgen Jelstad also conducted a short Q&A session with Dr Fluge –

Q & A
with
Olav Mella and Øystein Fluge

1. What is your current hypothesis for why Rituximab works?

Our working hypothesis has been, and still is, that ME/CFS might be an autoimmune disease. Maybe it should at this stage be called a disease of immune dysregulation, and inflammation probably also is a factor. So right now our hypothesis is that ME/CFS might be an autoimmune/autoinflammatory condition.

2. Why do most of the responding patients relapse after experiencing several months of improvement?
We do not yet know. But we see that with maintenance treatment some patients have a continuous major improvement lasting for months, even years. Another interesting observation is that some patients have a worsening of ME-symptoms right after the

infusion, which we must remember consists of a monoclonal antibody – an immunoglobulin. This worsening may last from a few days to some weeks. This reaction may tell us something important and be a clue to pathogenesis. There are no consistent correlations between B-cell numbers and relapses, but this is also the case with Rituximab treatment in RA. Another important thing to understand is why there is a latency period before response, where some patients get a response as early as six weeks, while others get the response only after 6-8 months.

3. What kind of follow-up studies are already underway?

We have one open label maintenance study on 28 patients. We promised the patients in the placebo group in the first RCT to be offered treatment if the study turned out positive, which it did, so this is an ethical responsibility. But most importantly, we want more experience and dose-response data before doing a larger RCT. If we get adequate funding, we plan to initiate a multicenter RCT in more than 100 ME/CFS patients. We also have one pilot study on six severely disabled patients, four of them mostly bedridden. And recently the ethical committee in Norway approved a pilot study trying a TNF-alfa inhibitor (Etanercept) on non-responders to Rituximab. And finally we are doing different studies on pathogenesis with a goal of finding biomarkers. In our biobank we have a lot of samples collected at several time points during our Rituximab studies, and we are attempting to unravel the mechanism behind the disease. From what we see in our studies, we feel confident that at least in a subgroup of patients the pathogenesis at some level will involve B-cells.

4. When do you expect to publish more results?

We hope to publish a few articles after this summer. We have done a lot of experiments on immune measurements, autoantibodies, gene expression etc. Some of the data are negative findings, but it is important that the negative data also get published to get the total view of what is happening.

5. Are you encouraged so far by what you see in the follow-up studies?

Yes, so far we have not discovered anything that undermines our previous findings. However, the disease probably is even more complex than we originally thought.

Jorgen Jelstad's book – De Bortgjemte – is currently only available in Norwegian. The charity hopes we can further influence the publishers to have the book translated into English as we feel it is currently the best book available to describe the political situation and the scientific situation surrounding ME.

ME STORY

I started to feel unwell about the age of 11.

I started to feel fatigue, headaches aching muscles, felt like I had the flu all the time and my speech went funny.

I went to the doctors and ended up in hospital. They didn't know what to do with me so I went to another hospital.

That's when my nightmare began.

I felt really ill at that time and a sister said it was all in my mind. I was left on a hard plastic chair all day. I was struggling to feed myself and my weight went down to 3 and a half stone because of the neglect that I had at that hospital.

I was close to death so my family took me out of that hospital.

It saved my life.

The disgusting treatment that I had at that hospital I could go on.

- Shelley

Current status of ME in Sweden

The Swedish ME/CFS Association, RME, was founded in 1993 and restarted in 2002 in order to support and spread information and knowledge about ME/CFS to patients and their families, to doctors, researchers, the public and authorities.

Today RME is a member of EMEA and has 944 members, 4 local associations and 12 supporting groups.

The National Board of Health and Welfare in Sweden has registered ME/CFS as a neurological disease – following the WHO ICD Classification. Despite that, very few patients get the diagnosis ME/CFS in our country.

In 2011, a book with the title "Fatigue is the wrong word" was written by 19 members, who all wrote their own medical history and described their present life. The book was completed with facts by doctors with ME/CFS experience. The book is today printed in 2100 copies. Of those we have sent more than 200 free copies to researchers, specialists, doctors, medical associations, medical advisers at The Swedish Social Insurance Agency and politicians all over the country. A translation from the book is found at the EMEA website.

There have been initiatives taken for establishing biomedical treatment for ME/CFS in some county councils in Sweden. Last year a ME/CFS-clinic in the county council of Stockholm/Danderyd was founded by Dr Per Julin. Per and his colleague Indre Bileviciute Ljungar will present their experiences at a seminar at Region Skane in autumn. In Ostergotland a ME/CFS-clinic, Gotahalsan, has been established by the neurologist Anders Osterberg. In Molndal near Gothenburg, the Gottfries Clinic accepts patients suffering from ME/CFS or fibromyalgia. Several county councils are interested in starting care units.

A Swedish network of researchers for biomedical ME/CFS research has been founded by among others Professor Emeritus Jonas Blomberg, Clinical Virology, Uppsala University, Professor Jonas Bergquist, Analytical Chemistry, Uppsala University, Dr Per Julin, Danderyd Hospital and Post Doc Yenan Bryceson, Center for Infectious Medicine, Karolinska Institutet. Professor Jonas Bergquist published in 2011, with a group of researchers, a study about protein profiles in the cerebrospinal fluid in ME/CFS patients. This study received much attention.

Riksföreningen för ME-patienter, Sweden
http://www.rme.nu/

The European ME Alliance (EMEA www.euro-me.org) is a collaboration of ME support charities and organisations in Europe who intend to provide a common view and the scientific facts regarding the neurological illness myalgic encephalomyelitis (ME/CFS).

EMEA are campaigning for funding for biomedical research to provide treatments and cures for ME. The alliance was formed in 2008 by national charities and organisations in Europe. The Alliance now has representatives from Belgium, Denmark, Germany, Holland, Ireland, Italy, Norway, Spain, Sweden, Switzerland and the UK. The alliance has been created with a basic set of principles to provide a correct and consistent view of myalgic encephalomyelitis (ME/CFS) for healthcare organisations, healthcare professionals, government organisations, the media and patients and the public.

Our objective is to establish a UK Centre of Excellence for Biomedical Research into ME. We welcome all support. Donations to the Invest in ME Biomedical Research Fund will be used to support the establishment of this facility. Help us by contributing to the Invest in ME Biomedical Research Fund for ME – http://tinyurl.com/ydh6whu

Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Fibromyalgia (FM) with a Staphylococcus Vaccine

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Background

The general scientific strategy evolved from a seminal observation made by professor Gottfries in 1958. He then noticed an increasing number of patients in his clinical psychiatric practice presenting a fatigue condition similar to the syndrome that in the 1990ies was named chronic fatigue syndrome or myalgic encephalomyelitis (ME/CFS). The patients continued to have a status indicating ongoing mild infection long after they had recovered from the Asian flu, an influenza which was epidemic in Sweden in 1958. This observation led to attempts of treatment with vaccine compounds in order to modulate/stimulate the immune system and thereby improve the status of the patients. Clinical benefit was noted in some individuals after repeated treatment with a staphylococcus toxoid vaccine (Gottfries, 1999).

Based on this uncontrolled experience, the vaccine treatment was reuptake in the 1990ies, when the diagnoses of ME/CFS and also the Fibromyalgia syndrome (FM) were established within medicine. The vaccine used in the clinical research, Staphypan®, contained a mixture of staphylococcal vaccine and toxoid. It was manufactured by the Swiss Serum and Vaccine Institute Berne until 2005 and used for the prophylaxis of staphylococcal infections, especially before surgery.

Controlled clinical studies

The first controlled double blind study was conducted in 1997 and included 28 patients (Andersson et al. 1998). The study drug, Staphypan or coloured sterile water as placebo, was administered subcutaneously on weekly basis. The start dose of 0.1 ml was increased by 0.1 ml every week up to 1.0 ml. Endpoint ratings were performed at week 12. Observer-based rating scales (CPRS-15) were used for the primary assessment of outcome. Significant beneficial effect was seen in favour of active treatment and the drop-out rate was low.

Encouraged by the positive results a second extended trial was performed.

This was a 6-month randomised controlled study, including 100 women fulfilling the criteria of combined ME/CFS and FM (Zachrisson et al. 2002). The study drug (Staphypan/coloured sterile water) was administered subcutaneously in doses of 0.1 to 1.0 ml at weekly intervals for eight weeks and then in booster doses of 1.0 ml every 4th week. End-point ratings were performed at week 26. Main outcome measures were proportion of responders on global ratings and proportion of "good responders", defined as patients with a symptom reduction of ≥50% from baseline in ratings on an observer-based rating scale (CPRS-15). Blind ratings were repeated at week 32 for evaluation of withdrawal effects.

The treatment was well tolerated (drop-out rate 8%) and 65% responded to active treatment. The placebo response was 18% ($p < 0.001$). Patients on active treatment were significantly more often "good responders". At withdrawal, deterioration was seen in the Staphypan group only, indicating the need of long-term treatment in order to maintain the effect. The majority of participant wanted to restart the treatment after the study.

Working mechanism

The clinical positive response to vaccine treatment was found related to the response of the patient's immune system.

In corporation with Professor Roland Möllby, the Karolinska Institute, the antibody status during treatment was evaluated (Zachrisson et al. 2004). In 14 patients receiving active vaccine treatment and 14 receiving placebo, the serological antibody status against extracellular toxins/enzymes, cell-wall components, and enterotoxins was evaluated at baseline and after six months of treatment.

Significant changes were recorded in the group on active treatment while no change was seen in the controls. Treatment led to an increase in the capacity of serum to neutralize alpha-toxin ($p< 0.001$) and led to a significant increase in serum IgG to alpha-toxin ($p< 0.01$) and lipase ($p< 0.01$). Furthermore, the increase in the serum parameters paralleled the improvement in clinical out-come. Thus, the greater the serological response, the greater was the clinical effect. This relationship could indicate a working mechanism of the vaccine.

Long term treatment In long-term studies the safety of the treatment were found good and the adherence to the treatment were impressive (Gottfries et al. 2006). In one follow-up study, 160 patients with FM and ME/CFS were continuously observed during another year of treatment. The patients had previously participated in controlled vaccine studies and were continuing on vaccine treatment with 1 ml Staphypan every 3rd to 4th week. At inclusion the mean treatment period with Staphypan was 22±10 months. The mean age of the patients was 53±11 years. The rating scale CPRS-15, handled by medically educated and trained staff, was used to evaluate efficacy. Ratings at inclusion showed improvement compared to start of treatment. Repeated ratings during the one year follow-up period showed further improvement. The total mean rating CPRS-15 score was reduced by more than 50 % compared to start of treatment. Five items (Concentration difficulties, Failing memory, Irritability, Sadness and Autonomic disturbances) had mean levels below one (range of scores 0-6) at the time of the last rating, indicating that these symptoms on a group level were within the range of normality. In a somewhat younger subgroup of 97 patients (age 48±10 years) with a mean treatment time of 50.4±17.8 months (variance 30-120), nine CPRS-15 core items were rated before as well as during treatment with the vaccine. They were analyzed with Principal Components Analysis (PCA) and a model was created using the clinical rating data at patient inclusion together with the assumed healthy profiles (Gottfries et al. 2009). The patient profiles after start of treatment were predicted by the PCA model and overlaid for comparison. The predicted values show loadings (black triangles in Figure), which have changed clearly in direction towards the normal group indicating improvement. The data show that this subgroup of middle-aged women after four to five years' treatment still has an impressive beneficial effect.

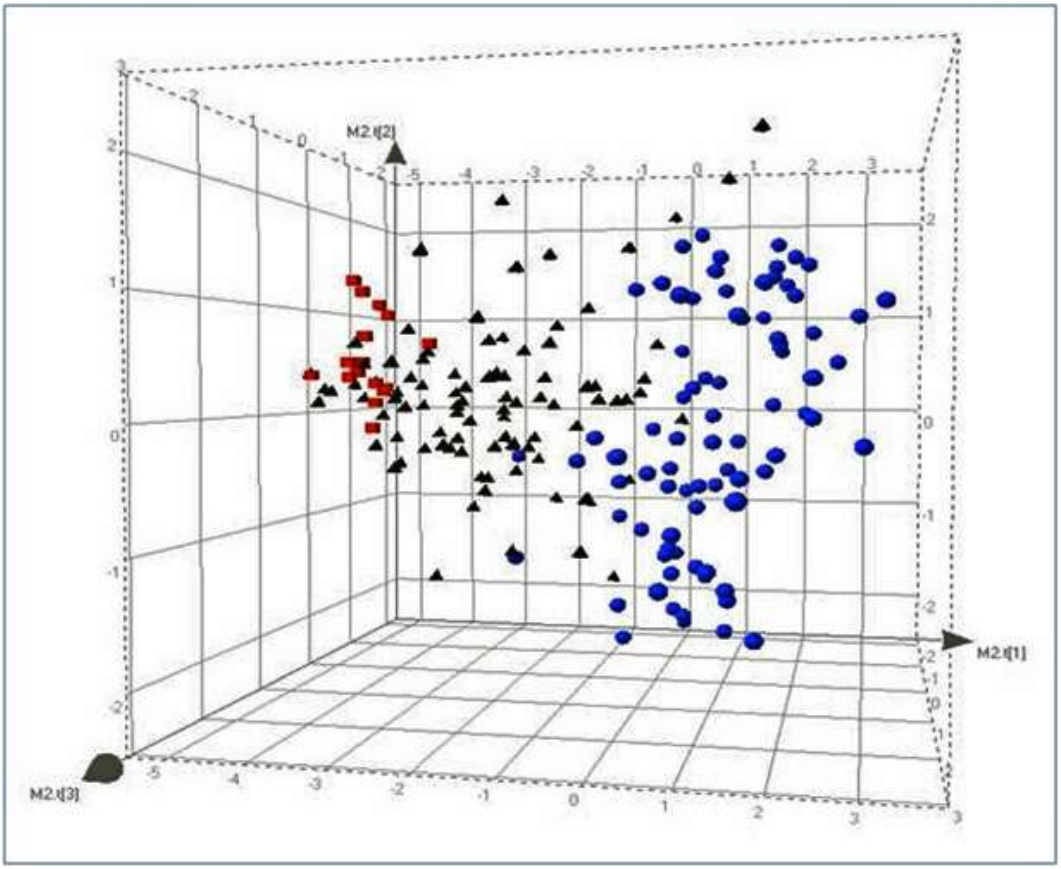

FIGURE
Scatter plot indicating PCA scores for the model. Red boxes indicate assumed healthy objects. Blue points for untreated patients as rated at inclusion. ▲ Black triangles for treated patients.
Each patient was re-assessed with last rating 50.4±17.8 months after study start (n=97) and his or her individual ratings predicted by the PCA model. The distribution after treatment with vaccine (black triangles) showed a shift of patient scores towards symptom relief.

Adverse events during long-term treatment
Safety was evaluated continuously. Adverse events were few and the adherence to the

treatment was surprisingly fine. During the observation period of one year on 160 patients, 22 of them (14%) withdrew from treatment.
Very few side effects were seen in relation to the treatment and no severe complications were recorded. According to the manufacturer, the vaccine had been used in more than 10 million dosages over the years, and no severe complications have been reported.
Our clinical impression is that a majority of patients with FM/CFS are prone to infections. In many cases patients also have an irritable bowel. The clinical impression was that the frequency of infections and symptoms of irritable bowel were reduced during long-term treatment. Our patients found the increased resistance to infections of great value.

In 2005 Staphypan was withdrawn from the market. Staphypan was an old product where the manufacturing process had to be developed to cope with modern GMP standards in EU and US. We have tried to find a vaccine that could replace Staphypan but there is no such product at least in the western world. We would assume that a vaccine treatment of the kind presented here eventually due to a super-antigen effect can be of use for patients with ME/CFS, FM and possibly other immune deficiency syndromes.

Conclusions

ME/CFS is a disorder of unknown aetiology. In controlled investigations it was shown that an immunotherapy, as conveyed by repeated injections of a staphylococcus vaccine preparation, Staphypan, was of clinical benefit for a significant number of patients. The effect was seen at the time when the treatment dose of Staphypan has been increased to 1 ml, the maximum dose used in our studies. The treatment was continued long-term with booster injections of 1 ml vaccine every 3rd to 4th week in order to maintain the effect. The treatment was found safe and the adherence to the treatment was impressive.

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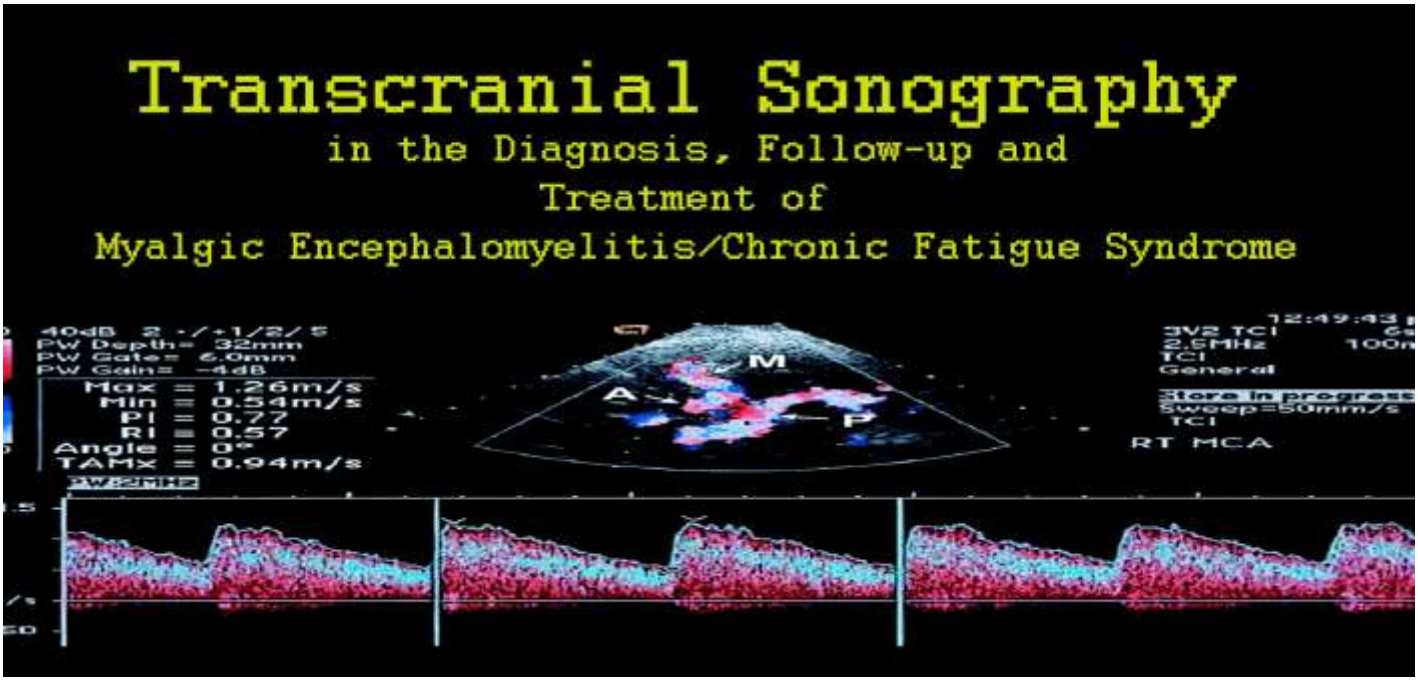

Transcranial sonography in the diagnosis, follow-up and treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Abstract

We used a modified transcranial sonography technique to study the cortex of the temporal lobe, a brain region involved in the processing of functions that are often compromised in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) patients. We studied the meninges, the subarachnoidal space and the cortex. The spatial resolution and the ability to visualize structures of 200-300 µm size, led us to hypothesize that the linear structures parallel to the subarachnoidal space could be referred to the neuronal layers of the cortex. In real-time mode, we could observe pulsation of the meninges and the cortex synchronous with the heart beat and independent of blood flow. This pulsation was more evident at the level of the meninges, but it was also appreciable at the level of the layers of the cortex and it was not accompanied by any type of flow. In addition to these findings, we observed that the subject undergoing the procedure experienced a series of changes that might prove potentially useful in the treatment of ME/CFS. In particular, we observed a decrease of tachycardia accompanied by an increase in systolic blood pressure and by a significant increase in muscle strength measured by the degree of muscle fibre shortening at the level of the biceps brachii. These findings, together with the low cost and simplicity of the procedure, suggest that modified transcranial sonography has a significant potential in the study and treatment of ME/CFS.

Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) designates a clinical condition characterized by a complex simptomatology that includes, but is not limited to, long-lasting disabling fatigue. According to the most recent classification, it is considered a neurological disease in the World Health Organization's International Classification of Diseases (ICD G93.3) and it is characterized by widespread inflammation and multisystemic neuropathology (1). As of today, the aetiology of ME/CFS is unknown and, just like in any syndrome, it is quite likely that there may be multiple causes leading to a shared clinical picture. Several events may act as triggers, from external environmental or microbiological triggers, such as chemical exposure or infections, to psychological and social factors that may be critical in perpetuating the symptoms (2). It is worth noting that from the point of view of evolution of the human brain, ME/CFS may be defined as a "phylogenic disease" (3-7), according to principle of "integrated phylogeny" of the primate brain (8), because of its possible relation to evolution.

For patients as well as for health care professionals, the issue of treatment of ME/CFS is a truly dramatic and controversial one. In fact, proposed treatments are as diverse as cognitive behavioral interventions (9), coiling dragon needling and moving cupping on back (10), treatment with Lactobacillus acidophilus (11), or with antipsychotics (12), just to name a few of the most recent studies.

Oddly enough, among the variety of proposed treatments for ME/CFS, the application of transcranial ultrasounds by means of a common ultrasound imaging machine has not been evaluated so far. A search of the literature revealed that transcranial sonography had been used as a diagnostic tool only in one study describing cerebral and systemic hemodynamic changes during upright tilt in CFS (13). However, in that study, the Authors were focussed on observation of the middle cerebral artery using transcranial doppler monitoring, and did not use probes and techniques able to study in detail the cerebral cortex with particular reference to the gray matter of the temporal lobe. Based on our background in clinical radiology and anatomy, we were interested in studying the cerebral cortex of the temporal lobe because of the well known involvement of the temporal lobe in the processing of functions, such as semantics and memory, that are often compromised in ME/CFS patients (14). To this end, we modified the conventional procedure for transcranial sonography and we used a linear probe that is normally used for muscle-skeletal ultrasound imaging. To our surprise, we observed that not only such a procedure allowed detailed visualization of the cortex of the temporal lobe, a finding potentially important for the diagnosis and follow-up of ME/CFS patients, but also affected brain function in such a way that it could be proposed as a safe and easy treatment for a variety of diseases including ME/CFS.

Materials and Methods

The ultrasounds used for imaging, also known as sub-thermal ultrasounds, are is considered safe and have been used for foetal imaging in utero, and virtually every part of the body, including brains of newborn babies through fontanelles. For transcranial sonography we used an Esaote MyLabFive ultrasound imaging machine approved for many applications including cephalic (brain) imaging. We used the default settings for adult transcranial imaging, but instead of a transcranial probe, we used a conventional linear probe for muscle-skeletal examination and we selected 7.5 MHz frequency. Acoustic power was set to 1.0. The length of the probe was about 4 cm, *i.e*. much less than the size of the temporal cortex that we examined that is 7-8 cm. The procedure was performed at the Laboratory for Exercise Sciences Applied to Medicine of the University of Firenze (LSMAM, Director, Prof. M. Gulisano).

The volunteer healthy subject, a certified clinical radiologist (M.R.), sat in front of the imaging machine in the position he normally uses to perform an examination, and positioned the probe on his right temporal region in correspondence of the acoustic window of the temporal squama (Fig. 1). An improvised support to his right arm was provided to ensure stability. In this position, the subject was able to look at his own brain while performing the examination. Heart rate was recorded 10 min prior to the transcranial sonography procedure, immediately before, during the procedure at intervals of 30 s, at the end of the procedure that lasted 10 min, and 10 min after the end of the procedure. Systolic and

diastolic blood pressure were recorded 10 min prior to the procedure, immediately before, at the end of the procedure, and 10 min after the end of the procedure. Thickness of the biceps brachii was measured with the same probe, but this time with the conventional setting for muscle-skeletal examination.

Results

During 10 min transcranial sonography, no side effect was reported. The parameters adopted for visualization of the temporal cortex allowed to distinguish the meninges, the subarachnoidal space and the cortex (Fig. 2). The meninges appeared as a well organized array of layers of about 5 mm thickness. The thickness of the cortex (3.8 mm) led us to hypothesize that we were observing the temporal areas designated as TG and TE, *i.e.* those areas involved in the control of eye movements and balance in standing position (area TE), social behaviour, mood and decision making (area TG). It is worth remembering that most of these functions are altered to various degrees in ME/CFS patients' symptoms (2). The spatial resolution and the ability to visualize structures of 200-300 µm size, led us to hypothesize that the linear structures (alternate gray-white stripes) parallel to the sub-arachnoidal space could be referred to the well known neuronal layers of the cortex (15). Considering the role of neuronal layer architecture alterations in neurodegenerative diseases (16), detailed study of these layers in ME/CFS might prove instrumental in diagnosis, prognosis and follow-up. With this type of setting and using Doppler technique, we could also observe arterial vascularisation of the meninges and pulsating arteries of less that one mm diameter could be easily visualized (Fig. 3). During transcranial sonography, we could also observe a peculiar pulsation of the meninges and of the cortex that was synchronous with the heart beat, but was not accompanied by any type of flow. This pulsation was more evident at the level of the meninges, but was also appreciable at the level of the layers of the cortex. A similar type of pulsation was described in 1987 by Klose et al. who used Magnetic Resonance Imaging to study the oscillation of the cerebrospinal fluid within the cardiac cycle (17). We have no evidence, as yet, that the observed pattern of brain pulsation may be altered in ME/CFS patients nor that this observation may contribute to diagnosis or follow-up. However, the easy reproducibility of the procedure as well as the absence of any discomfort, render this type of approach worth of further investigation. In fact, it was proposed that alteration of the so-called cranial rhythmic impulse might have a role in the pathogenesis of ME/CFS (18), and spinal fluid abnormalities are common in ME/CFS patients (19).

Although the primary goal of our research was to set up a technique to study brain morphology and function in ME/CFS patients, while performing transcranial sonography with the indicated setting, we noticed that some notable changes happened in the subject who was at the same time the operator of the echo machine and the object of observation. In fact, an ill-defined feeling of strength and well-being that had been reported during the first measures prompted us to further investigate whether the ultrasounds used for imaging could somehow affect brain function. The use of transcranial ultrasounds in both military and civilian settings to stimulate the central nervous system has been recently proposed (http://www.darpa.mil/Opportunities/Universities/Young_Faculty_Award_Recipients.aspx) (20), and a preliminary study performed at the University of Arizona demonstrated that transcranial ultrasound stimulation improved mood and increased heart rate, systolic and diastolic pressure and decreased oxygen saturation (http://www.quantumconsciousness.org/documents/ATUS201101634A.pdf). In the study reported above, however, transcranial ultrasound application was performed by an operator and the subject being investigated did not look at his own brain while performing the procedure. This difference might be significant because of the ensuing bio-feedback, an effect that has proven effective in a variety of conditions from neurological disorders to cancer (21, 22).

In our study, we observed that heart rate significantly decreased from 81 beats per minute (bpm) at the beginning of the procedure to 71 bpm at the end of the procedure, to 70 bpm 10 min after the end of the procedure. Systolic blood pressure increased from 115 mm/Hg (10 min before the procedure) to 125 mm/Hg (10 min after the end of the procedure). Unlike the study quoted above, diastolic pressure did not change and remained constant at 75 mm/Hg before and after the procedure. It is well assessed that cardiovascular symptoms and hypotension are

common in ME/CFS patients (23), and it has been suggested that hypotension associated with orthostatic stress may impair neurocognitive functioning in ME/CFS patients with postural tachycardia syndrome (24). Therefore, our results as well as those presented by Hameroff et al. (http://www.quantumconsciousness.org/documents/ATUS201101634A.pdf) may lead to interventional applications of transcranial sonography in the treatment of orthostatic intolerance, one of the major symptoms of ME/CFS.

The observed increase in systolic blood pressure in the absence of a concomitant increase in heart rate or diastolic pressure, is of particular significance for ME/CFS, and it can be interpreted as if transcranial sonography was associated with increased cardiac output; in particular, as if it increased the stroke volume, an index that is frequently decreased in ME/CFS patients and is associated with the most common symptoms reported in ME/CFS, *i.e*. shortness of breath, dyspnea on effort, rapid heartbeat, chest pain, fainting, orthostatic dizziness and coldness of feet (23). The observed decrease in heart rate might also prove useful in those ME/CFS where tachycardia is a symptom associated with neurocognitive defects (25).

In order to determine the anatomical correlate of the subjectively perceived increase in muscle strength, we measured by ultrasonography the thickness of the biceps brachii in relaxation and maximal contraction, before and after transcranial sonography (Fig. 4).Ten min before transcranial sonography, the thickness of the biceps increased from 24.9 mm (Fig. 4, panel A) to 38.3 mm during maximal contraction (Fig. 4, panel B). Ten min after the end of the procedure, the thickness of the biceps increased from 24.9 mm (Fig. 4, panel C) to 43.2 mm (Fig. 4, panel B). The increase in thickness was accompanied by a concomitant increase in the angle between the muscle fibres and the muscle aponeurosis. These results demonstrate that the subjectively perceived increase in muscle strength was indeed associated with a measurable increase in the capacity of the muscle to contract with significant increase in muscle fibre shortening.

Discussion

The results presented in this study raise the possibility of using transcranial sonography as a tool for the diagnosis, follow-up and treatment of ME/CFS patients. In recent years the cost of ultrasound imaging machines is significantly decreased and a good quality apparatus is now sold (in the year 2012) for about 20.000,00 Euros. In the hands of properly trained health care professionals the procedure of transcranial sonography described here can be used for the study of brain pulsations and/or rhythmic impulses and for the study of vascularisation of the meninges. Furthermore, considering that significant neuroanatomical changes occur in ME/CFS, and that these changes are consistent with impaired memory (26), transcranial sonography may prove a simple and inexpensive tool to assess these changes and monitor progression of the disease as well as improvements associated with treatments. The inherent safety of the technique as well as the absence of discomfort make this procedure quite acceptable by patients and this characteristics may prompt extensive studies on a significant number of patients.

In addition to its use a tool contributing to diagnosis and follow-up, our results suggest that transcranial sonography may also prove useful in controlling some of the most disturbing symptoms of ME/CFS, *i.e*. chronic pain and mood alterations as demonstrated by Hameroff et al. ((http://www.quantumconsciousness.org/documents/ATUS201101634A.pdf), hypotension, tachycardia and muscle weakness.

Figure legends

Figure 1. The operator (M.R.) applying the probe to his right temporal region. Sitting in front of the ultrasound imaging machine, the operator is able

to observe his own brain in real time. In this way it is possible to observe brain pulsations as well as blood flow through meningeal arteries. We hypothesize that direct observation of the brain triggers a bio-feedback effect.

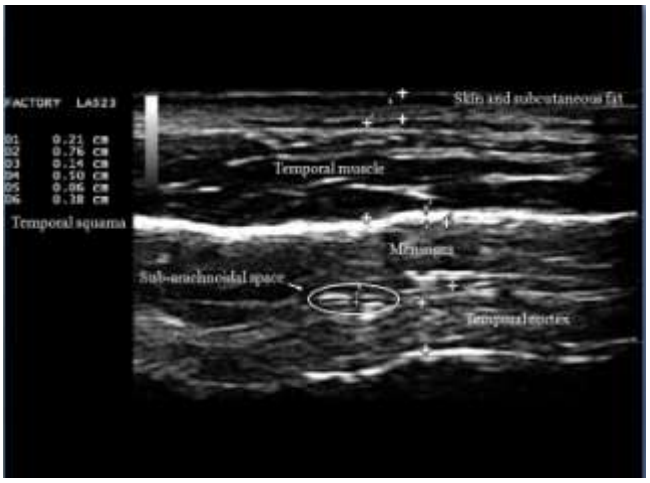

Figure 2.
Two dimension image of the temporal region. The skin layers and the temporal muscle are clearly visible. The temporal squama appears as an hyper-reflecting (white) irregular line of about 1.4 mm thickness. The meninges appear as a well organized array of layers of about 5 mm thickness. The sub-arachnoidal space (white arrow) is identified by two hyper-reflecting (white) lines sandwiching an hypo-reflecting (black) space containing liquor. The size of the sub-arachnoidal space was about 0.6 mm. The neuronal layers of the temporal cortex (3.8 mm thickness) appear as alternate layers of hyper- and hypo-reflecting structures. The thickness of the cortex corresponds to that of the TE and TG areas.

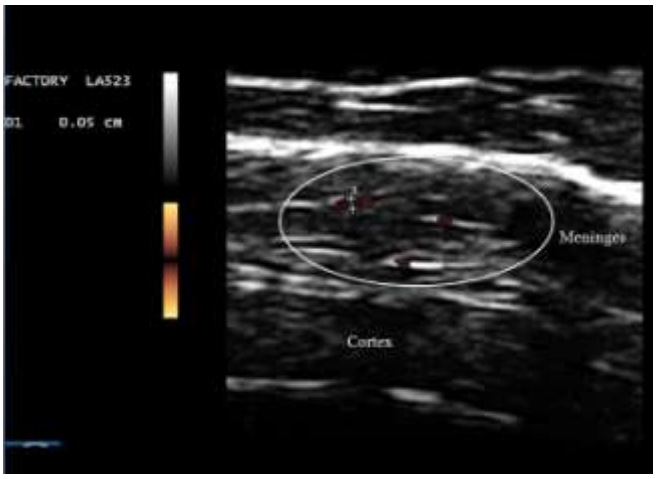

Figure 3. Pulsating arterial blood vessels in the meninges.

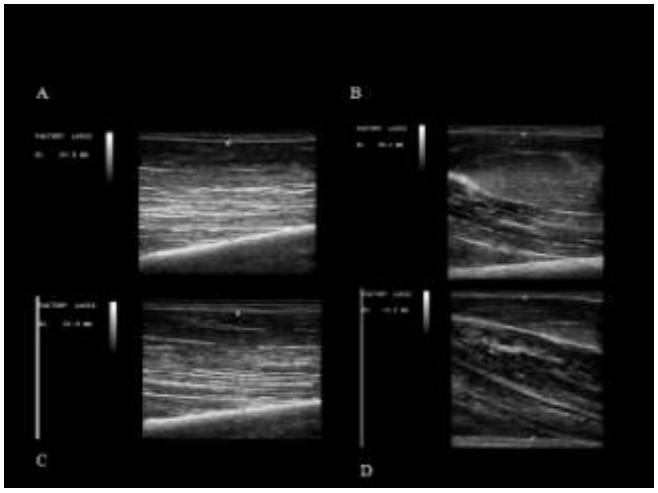

Figure 4.
Two dimension image of the left biceps brachii. Also in this case the operator applied the probe to his own biceps.
A. Thickness of the relaxed biceps 10 min before the procedure; 24.9 mm.
B. Thickness of the contracted biceps 10 min before the procedure; 38.3 mm.
C. Thickness of the relaxed biceps 10 min after the procedure; 24.9 mm. Please notice; this image is not the same shown in panel A, as clearly visible looking at the orientation of the fibres. Nevertheless, the measurement is identical, thus demonstrating the reproducibility of the procedure.
D. Thickness of the contracted biceps 10 min after the procedure; 43.2 mm.

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ME COMMENT

"Respondents found the least helpful and most harmful interventions were Graded Exercise Therapy and Cognitive Behavioural Therapy" Norfolk and Suffolk ME Patient Survey 2009 http://www.norfolkandsuffolk.me.uk/surveylink.html

THE IMMUNOLOGICAL BASIS OF ME/CFS: what is already known?

A compilation of documented immune system abnormalities in ME/CFS from 1983-2011

by Margaret Williams
March 2012

Introduction

There can be few practising health care professionals in the UK National Health Service who are unaware of the contentious battleground in which the disorder myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) remains mired even though it has been formally classified as a neurological disorder by the World Health Organisation since 1969, currently at ICD-10 G93.3.

Essentially, there are two camps, one consisting of internationally renowned medical scientists and clinicians who acknowledge that ME/CFS is a multi-system neuro-immune disorder with protean symptomatology and who understand the extensive and compelling biomedical evidence-base that underpins the demonstrated organic pathophysiology.

Given the extent of this international peer-reviewed published evidence, one would have thought that no competent medical scientist, clinician or medical journal could credibly deny or reject the evidence that ME/CFS is a disorder of disrupted immune function, yet this continues to be the case.

The second camp, a small group of UK psychiatrists and their adherents known as the "Wessely School" (Hansard: Lords: 9th December 1998:1013) choose to ignore this body of scientific evidence and they continue to subsume ME/CFS within their own construct of "CFS/ME" (which they insist is the same as "ME/CFS" or "ME" or "CFS" alone) and is defined by them as "*medically unexplained chronic fatigue*". They assert that it is a functional (behavioural) disorder resulting from wrong attributions so is curable by "*cognitive restructuring*" (a form of brain washing intended to convince patients that they do not suffer from a physical disease but from "*aberrant illness beliefs*"), together with graded exercise to reverse their alleged "*deconditioning*". The Wessely School believe that the more symptoms of which a patient complains, the greater the confirmation that s/he is suffering from a psychogenic disorder and that the distressing symptoms are merely "*hypervigilance to normal bodily sensations*" and to "*the perception of visceral phenomena*" (The Cognitive Behavioural Management of the Post-viral Fatigue Syndrome; S Wessely, et al; In: Post-Viral Fatigue Syndrome, ed. Rachel Jenkins & James Mowbray, John Wiley & Sons, 1991, page 311; Professor Peter White: Presentation to the British Neuropsychiatry Association, St Anne's College, Oxford, December 2008).

As key members of the Wessely School are advisors to Departments and agencies of State, it is their term and interpretation that is used by those agencies, as the Wessely School's influence appears to be without limit when it comes to this disorder.

The Wessely School's intention is known to be to "eradicate" ME by dropping the "ME" from "CFS/ME" when expedient (Pfizer/Invicta: 4-5 /LINC UP, 15th April 1992; BMJ 2003:326:595-597) and then to reclassify "CFS" as a "functional" or behavioural disorder in the forthcoming revisions of both the WHO's International Classification of Diseases (ICD–11) and the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5).

Most of the Wessely School members also work for the permanent health insurance industry and have demonstrable financial interests in claiming "CFS/ME" as a functional disorder, since functional disorders are excluded from benefit payment. This unacceptable situation has for some years caused grave parliamentary concern (http://erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf).

Notwithstanding, Professor Wessely has just published a paper in the Journal of Neurology, Neurosurgery and Psychiatry in which he appears

to favour deliberately deceiving patients: "*The term 'functional' has increasingly come to mean 'hysterical'…The DSM-V working group* (which includes Professor Michael Sharpe from the UK, a prominent member of the Wessely School) *proposes to use 'functional' as the official diagnostic term for medically unexplained neurological symptoms (currently known as 'conversion disorder')….Interviewing the neurologists in a large UK region and then surveying all neurologists in the UK on their use of the term, (the interviews) revealed four dominant uses – 'not organic'; a physical disability; a brain disorder and a psychiatric problem – as well as considerable ambiguity….The ambiguity was seen as useful when engaging with patients. The survey (found) a majority adhering to a strict interpretation of 'functional' to mean only 'not organic'…. 'Functional' can, for example, be used to mean a disturbance of bodily function or it can be used to denote conversion disorder; and by telling a patient they have a 'functional disorder' they may encourage them to contemplate the former meaning, without being aware of the latter … There is a divergence between the terms neurologists use medically and with lay people. One advantage of 'functional' (allows) neurologists to use the same term to mean one thing to colleagues and another to patients….Its diversity of meaning allows it to be a common term while meaning different things to different people….and thus conceal some of the conflict in a particularly contentious area"* (JNNP 2012 Mar;83(3):248-250).

Further muddying the waters is the fact that the Wessely School use their own case definition of "CFS" (the "Oxford" criteria: JRSM 1991:84:118-121) and they intentionally include within their terms "CFS" or "CFS/ME" those with chronic "fatigue" or on-going tiredness. Indeed, in the notorious £5 million PACE Trial, the Chief Principal Investigator, Professor Peter White (another prominent Wessely School member), stated at section 3.6 of the Trial Identifier: "*Subjects will be required to meet operationalised Oxford criteria for CFS. This means six months or more of medically unexplained, severe, disabling fatigue affecting physical and mental functions.* ***We chose these broad criteria in order to enhance generalisability and recruitment".*** Deliberately to broaden entry criteria for a clinical trial purporting to be looking at people with ME whilst including patients who do not have the disorder in question would seem to contravene elementary rules of scientific procedure.

The Wessely School have for decades dismissed the need to sub-group "CFS": the UK Chief Medical Officer's Working Group 2002 Report (Annex 4: section 3) with which they were involved asserts that sub-grouping "*may be considered a matter of semantics and personal philosophy*", but biomedical experts have long called for sub-grouping in order to better understand the pathophysiology and to more effectively direct therapeutic interventions, since it has been shown that ME/CFS patients with a particular immune dysfunction do not respond favourably to exercise.

Given the extent of the international peer-reviewed published evidence that proves these psychiatrists to be wrong, it is reprehensible that the medical journals for which they serve as peer-reviewers and the agencies of State to which they are advisors continue to permit their disproven beliefs about ME/CFS to remain unchallenged, with the result that patients with ME/CFS continue to suffer iatrogenic harm.

It was eighteen years ago that Professor Paul Levine from the Division of Cancer Aetiology, National Cancer Institute, Bethesda, Maryland, pointed out that: ***"In the study of a complex illness such as (ME)CFS, the most important aspect is case definition….The spectrum of illnesses associated with a dysregulated immune system now must include (ME)CFS"*** (Paul H Levine. Clin Inf Dis 1994:18 (Suppl 1):S57-S60).

In October 2009, Nancy Klimas, Professor of Medicine and Immunology, (then at the University of Miami) and one of the world's foremost AIDS and ME/CFS researchers said: ***"I hope you are not saying that (ME)CFS patients are not as ill as HIV patients. I split my clinical time between the two illnesses, and I can tell you that if I had to choose between the two illnesses I would rather have HIV"*** (New York Times, 15th October 2009).

In the autumn of 2011, commenting on and supporting the Norwegian study by Drs Fluge and Mella that used the anti-cancer drug Rituximab with good effect in ME/CFS patients (PloS ONE

October 2011:6:10:e26358), Professor Klimas said: ***"Many clinicians fail to realise the severity of the illness that has been termed ME/CFS. This is a profoundly ill population"*** (http://bergento.no/the-mecfs-study-by-mella-and-fluge-is-a-key-study-for-our-field).

The situation in the UK is a travesty of both medical science and human rights; things have become so serious and patients with ME/CFS in the UK are so neglected – indeed, they are treated with undisguised contempt and are abused by those working in the very system that is designed to support them -- that discussions are taking place concerning the European Commission on Human Rights, as the Human Rights Act is intended to protect people from neglect and abuse, whatever the source.

In summary, reproducible laboratory immunological abnormalities in ME/CFS include very low numbers of NK cells, with decreased cytolytic activity; circulating immune complexes (two-thirds of ME patients have circulating immune complexes, which are insoluble and can remain trapped in blood vessels and tissues); autoantibodies, especially antinuclear and smooth muscle; increased T4:T8 ratio facilitating allergies and hypersensitivities (which always corresponds with disease severity); abnormal SIgA; positive IgG3 (linked to gastrointestinal tract disorders); positive IgM (in his Medical Address at the AGM of the ME Association on 25th April 1987, James Mowbray, Professor of Immunopathology, St Mary's Hospital Medical School, London, said: *"If someone has IgM antibodies they have either been recently infected or they are still infected*"); and a particular HLA antigen expression.

Given the extent of the Wessely School's involvement with (and influence over) State policy for ME/CFS, it is notable that, on his own admission, Professor Wessely does not understand immunology. On 10th August 2004 in his evidence to the Lord Lloyd of Berwick Independent Inquiry into Gulf War Illnesses, when discussing immunology and the shift from Th1 to Th2 (as has been shown to occur in ME/CFS also), Wessely said: "*Now, please do not ask me what that means because I do not really know. A man has got to know his limitations and my limitations are immunology"* (www.lloyd-gwii.com/admin/ManagedFiles/2/GWI1008%2000.doc). It must also be recalled that the 1996 Joint Royal Colleges' Report on CFS (in which Wessely School members were instrumental) specifically recommended that no investigations should be performed to confirm the diagnosis (page 45) and that immunological abnormalities *"should not focus attention…towards a search for an 'organic' cause"* (page 13), or that Wessely advises that "*Unhelpful and inaccurate beliefs about CFS include the following…CFS is due to a persistent virus or…immune disorder"* (Update, 20th May 1998:1016-1026).

Documented immune system abnormalities in ME/CFS

There is an extensive and significant published evidence-base of reproducible immune dysfunction in ME/CFS. All are important, as they show that for the last 30 years immunological problems have been known to underpin ME/CFS. (Note that for reasons of space, extracts are sometimes sequentially condensed).

It must be remembered that there are equally undeniable evidence-bases on the documented abnormalities observed in the neurological system (central, autonomic and peripheral, including vestibular dysfunction), as well as in the endocrinological, cardiovascular, musculoskeletal, respiratory, gastro-intestinal and ocular systems, and also on the cognitive impairment that has been shown in ME/CFS; on the proven abnormalities that have been repeatedly demonstrated on nuclear medicine imaging, and in the abnormal gene expression in ME/CFS patients (indeed, one senior research scientist has stated that there are more abnormal genes in ME/CFS than in cancer).

Given the extracts below, readers may be shocked to learn that in 2012 in the UK, influenced by the Wessely School, immune system investigation of people with ME/CFS remains proscribed by NICE (the National Institute for Health and Clinical Excellence, to whose nominally "advisory" Guidelines clinicians are required to adhere on pain of losing their registration to practise medicine), and the only

interventions permitted are cognitive restructuring and graded exercise.

1983

"Our research and that of others working in collaboration with us has shown conclusively that post-viral fatigue state, i.e. myalgic encephalomyelitis, has an undisputed organic basis….We were also able to show by looking at receptors on lymphocytes i.e. markers on white blood cells, that there was an increased association of patients with the disease with one particular type of marker. ***This type of marker is usually found in patients with immunological abnormalities of a particular type. We furthermore were able to demonstrate that there was impaired regulation of the immune system in patients with the disease, both in the acute and chronic stage….we did this serially on several occasions and the abnormality persisted. The abnormality was..of the sort that is found with persistent virus infection. A number of other subtle but definite immunological abnormalities were found and described that…are of the type found in association with disorganised immunoregulation….This meeting at Cambridge showed that using… advanced immunological tests…that patients with myalgic encephalomyelitis had definite proven abnormalities of a specific type****"* (Dr – later Professor -- Peter Behan; consultant neurologist. Symposium on ME, Cambridge, September 1983).

1985

"Our detailed studies have uncovered a series of subtle yet objective organic abnormalities in these patients. Importantly, nearly all of the patients studied had increased T cell mediated suppression…which showed increased numbers of OKT4 positive (helper-inducer) cells" (Stephen E Straus, G Tosato et al. Ann Int Med 1985:102:7-16).

1986

"Eighty percent of patients demonstrate clinically significant IgE mediated allergic disease, including food and drug reactions. The data indicate that patients have a high association with hypersensitivity states. Percent positive responsiveness to allergens is consistent with the high degree of allergy observed in these patients" (George B Olsen, James F Jones et al. J All Clin Immunol 1986:78:308-314).

1986

"***We have now studied about 1000 samples from patients with ME….Virtually all of the samples of patients with a good clinical diagnosis of ME have circulating IgM complexes in their blood…In addition 25% of them have detectable IgM anti-Coxsackie virus antibodies in the blood.*** *These antibodies are made shortly after exposure and their presence after many years suggests that the exposure and the immunisation is continuing. In addition…it has been possible to show that about 40% of the patients have Coxsackie group specific antigens bound to the antibody in their blood. The majority of patients have high IgG titres of antibody to Coxsackie viruses as well"* (Professor James Mowbray's Report on Research on ME to the ME Association, June 1986).

1986

In his Foreword to Dr Melvin Ramsay's publication "Post-Viral Fatigue Syndrome – the Saga of Royal Free Disease", promoted and sold by the ME Association, Dr Peter Behan said: "*The disease follows viral infections, and* ***laboratories on both sides of the Atlantic have now provided convincing evidence that these patients do have histological, electrophysiological and immunological abnormalities".***

1987

Irving Salit, Associate Professor of Medicine and Microbiology at the University of Toronto and Head of the Division of Infectious Diseases at Toronto General Hospital, noted: "*Findings include mild immunodeficiency, slightly low complement, anti-DNA antibodies and elevated synthetase, which is an interferon-associated enzyme commonly increased in infections.* ***This illness is of major importance because it is so prevalent and because it has such devastating consequences: afflicted patients are frequently unable to work or carry on with usual social activities…****.Patients tend to tolerate medications very poorly and many have a history of drug allergies. Most patients do not improve on anti-depressants and are usually exquisitely sensitive to the side effects"* (Clin Ecol 1987/8:V:3:103-107).

1987

US clinicians and researchers who became world leaders in ME/CFS (including Drs Paul Cheney, Daniel Peterson and Anthony Komaroff) noted: "*These studies demonstrated that a majority of patients with (ME)CFS have low numbers of $NKH1^+T3^-$ lymphocytes, a population that represents the great majority of NK cells in normal individuals. (ME)CFS patients had normal numbers of $NKH1^+T3^+$ lymphocytes, a population that represents a relatively small fraction of NK cells in normal individuals. When tested for cytotoxicity against a variety of different target cells, patients with (ME)CFS consistently demonstrated low levels of killing. In humans, studies suggest a correlation between low NK activity and serious viral infections in immunocompromised hosts.* ***We have carried out extensive phenotypic and functional characterisation of NK cells in patients with this syndrome (and have) found that the majority had abnormally low numbers of $NKH1^+$ cells.*** *Further characterisation of such cellular subset abnormalities and the resulting alteration in quantitative and qualitative NK cytotoxic function will hopefully improve our understanding of the immunopathogenesis of this illness"* (M Caliguri et al. The Journal of Immunology 1987:139:10: 3306-3313).

1987

At the CFS Society, USA, conference held on 4^{th}-7^{th} November 1987, Dr Alfred Johnson said that 97% of ME/CFS patients have allergies and that allergic patients have high helper (T4) cells and low suppressor (T8) cells, causing over-reactivity. Dr Paul Cheney confirmed that the T4:T8 ratio is elevated in two-thirds of cases, and that this is considered a more reliable marker of the illness than other markers, saying that there are "*impressive abnormalities"* in mitogen stimulus status (an immune function test) and that symptoms are caused by a hyper-immune response.

1988

In the "News Focus" section of the Nursing Times, Pamela Holmes reported the view that (ME) PVFS is due *"to a variety of aberrant immune system responses involving monokines, lymphokines and abnormal interferon production and breakdown (and) a poorly functioning immune system"* (Nursing Times 1988 January 13:84:2:19).

1988

"This article summarises recent studies of the syndrome and emphasises our assessment of one of its more common manifestations, allergy. Many patients report inhalant, food or drug allergies. Allergies are a common feature of patients with the chronic fatigue syndrome. ***Among the features of this syndrome is a high prevalence of allergy, an allergy that appears to be substantial, both by history and by skin testing****"* (Stephen E Straus, Janet Dale et al. J Allergy Clin Immunol 1988:81:791-795).

1988

"A variety of immunological abnormalities were detected, including abnormal T4/T8 lymphocyte subset ratios, dysfunction of natural killer cells, abnormal proliferation of B cells and decreased IgG concentrations" (PO Behan, WMH Behan. Crit Rev Neurobiol 1988: 4:2:157-178).

1988

"*We report patients (who) had a specific deficiency of IgG1 subclass. The finding of IgG1 subclass deficiency in these patients is novel, as lone deficiency of this subclass is rare and affected patients appear to have common variable hypogammaglobulinaemia. Further scrutiny of cases (of ME/CFS) may reveal a range of subtle immunological abnormalities"* (Robert Read, Gavin Spickett et al. Lancet, January 30 1988:241-242).

1988

The ME Association's magazine "Perspectives" carried an article on "Viruses and ME" by consultant microbiologist Dr Betty Dowsett, who wrote: "*Many viruses (including enteroviruses) can enter and alter the function of the immune cells specially designed to destroy them. It is important to recognise that these immune abnormalities are <u>secondary</u> to the virus infection….The mopping up of free viruses in the bloodstream can be counter-productive if excess antibody is produced.* ***The insoluble 'immune complexes' that result can be***

trapped in the blood vessels and tissues and…maintain infection in the body….The chemical composition of a virus may mimic that of a normal body component (such as brain or muscle protein) whereupon the immune attack is misdirected against the host while the virus disappears unnoticed. Cardiac and other complications in ME are an example of such an anomaly*".*

1988

The June 1988 issue of The CFIDS Chronicle stated: "***Eminent physicians have publicly stated that this is primarily a disease of immune dysfunction and this is substantiated by the very significant immune abnormalities found in CFIDS patients by medical researchers. This is a 'real' illness of immune dysfunction****"*.

1988

"Lymphocyte phenotyping…has revealed several abnormalities. Dr Paul Cheney and others have found that the circulating suppressor T cell number is decreased in many CFIDS patients…In some CFIDS patients, the number of circulating B cells is reduced…Natural killer cell abnormalities in CFIDS patients have been reported….In addition, NK cells from CFIDS patients did not function as well as NK cells from normal individuals….In a controlled study conducted by a group of Australian researchers, T cell function…was decreased in over 80% of patients….Lymphokines are proteins which act as messengers for the immune system. Dr Paul Cheney and other researchers have found elevated levels of alpha interferon…Interleukin-2 levels have also been found to be elevated in many CFIDS patients….In conclusion, the results of several immune system tests are abnormal in CFIDS patients and indicate that there is immune dysfunction involved in this illness" (Susan E Dorman. The CFIDS Chronicle, September 1988).

1988

*"**On immunological testing, we and others (Dubois 1984; Jones 1985; Straus 1985; Tosato 1985; Olson 1986; Caliguri 1987) have found evidence of subtle and diffuse dysfunction: partial hypogammaglobulinaemia (25-80%); partial hypergammaglobulinaemia (10-20%); low levels of autoantibodies, particularly anti-thyroid antibodies and antinuclear antibodies (15-35%); low levels of circulating immune complexes (30-50%); elevated ratios of helper-suppressor T-cells (20-35%)…reduced in vitro synthesis of interleukin-2 and interferon by cultured lymphocytes; increased IgE-positive T and B cells; and deficient functional activity of natural killer cells. Some investigators have found increased levels of circulating interferon, whereas others have not. Straus demonstrated a significant increase in levels of leucocyte 2'5'-oligoadenylate synthetase activity, an enzyme induced during acute viral infections (Straus 1985)**"* (Anthony L Komaroff: Chronic Fatigue Syndromes: Relationship to Chronic Viral Infections. In: Persistent Herpes Infections: Current Techniques for Diagnosis; Ed: Gerhardt RF Krueger, Dharham Ablashi and Robert C Gallo; Pub: Elsevier Press 1988).

1988

A landmark conference/research workshop on (ME)CFS took place in September 1988 at the University of Pittsburgh; it was co-chaired by Seymour Grufferman, Professor and Chairman of the Department of Clinical Epidemiology and Preventive Medicine at the University of Pittsburgh and Stephen Straus, Head of Medical Virology at the National Institute of Allergy and Infectious Disease (NIAID). **Professor Grufferman used the term "chronic fatigue and immune dysfunction disease" (CFIDS) and commended the use of this term on the basis of the immune dysfunction that has been observed in this disorder.** Several researchers noted that the pathophysiology of (ME)CFS includes an inappropriate and/or inflammatory response (The CFIDS Chronicle, October 1988).

1988

"The Third International Symposium on Epstein-Barr Virus and Associated Malignant Diseases was held in Rome on 3rd – 7th October 1988. For the first time, scheduled presentations and a round table discussion on post-viral chronic fatigue syndrome (CFIDS, [ME]CFS) were included in the programme. Dedra Buchwald MD from the University of Washington presented an overview of the laboratory abnormalities which have been

*found in (ME)CFS patients….**Circulating immune complexes have been observed in an average of 59% of (ME)CFS patients….A decrease in NK cell number or percent has been observed in up to 75% of patients, and NK cell function has also been found to be diminished…The immunologic aberrations…support the hypotheses of an underlying organic pathology**".*

Drs Nancy Klimas and Mary Ann Fletcher et al noted the increase in numbers of a certain subset of B cells which are associated with autoimmune disease, concluding: "***Significant immunological abnormalities have been recognised in this group of (ME)CFS patients.*** *The possibility of an underlying immunodeficiency should be considered as a potential aetiological mechanism in the natural history of this syndrome"* (The CFIDS Chronicle, November/December 1988).

1989

Susan Dorman commented on the study by Drs Paul Cheney and David Bell that was published in The Annals of Internal Medicine 1989:110(4), noting that **average levels for IL-2 were significantly higher in (ME)CFS patients than for controls. The average serum IL-2 value for Dr Cheney's patients was 56.2 units per millilitre and for Dr Bell's patients the average serum IL-2 value was 55.5 U/mL. The average serum IL-2 for the controls was 1.4 U/mL. The normal range for the assay used is less than 5 U/mL.** "*This objective immune system abnormality may also help to legitimise the disease"* (The CFIDS Chronicle, January/February 1989).

The same issue noted the NIAID press release of 15th February 1989 which quoted Dr Stephen Straus: ***"Many physical and immunologic features of (ME)CFS cannot be explained by psychiatric illness"***. It also noted that in 1988 congressional hearings, Dr Anthony Fauci, NIAID Director (the NIAID being a division of the NIH) reported that the basis of CFIDS involves immunological aberrations.

The issue also carried an article by Dr Susan Levine from Mt Sinai Hospital Department of Immunology, New York, on "Allergy, Immune Function, and Endocrinological disorders in CFIDS" in which she said: *"Allergic manifestations are often seen hand in hand with certain immunodeficiencies, such as the absence of IgA and of specific IgG subclasses".*

1989

The UK ME Association published "Latest Research Findings" in March 1989: "*Dr Peter Behan in Glasgow has made some remarkable new findings about ME….Though B cells appear normal, they are lacking a particular antigen (an antigen is a substance that stimulates the production of antibodies). This abnormality appears to be unique to ME.* ***On measuring levels of Interleukin-1β (a chemical messenger of the immune system) in ME sufferers and comparing them with normal controls…it was found that the average level in the 'normal' control group was 20 titograms per ml*** (sic -- ? picograms/pg per ml)***, while in people with rheumatoid arthritis it was up to 51. In many people with ME it was around 20,000 (this is not a typographical error). IL-1β is known to turn on the production of other chemical messengers….act on the liver to displace protein production (and) decrease the white cell count….It appears from these findings that many ME sufferers have abnormalities of the immune system. In the case of IL-1β, so abnormal were the levels that the lab which was doing the measurements thought there had been a mistake***".*

1989

The San Francisco (ME)CFS Conference was held on 15th April 1989; notably, Dr Jay Levy, a well-known AIDS researcher at the University of California, informed healthcare professionals that CFIDS may be linked to the eventual development of multiple sclerosis (an autoimmune disease) and said "*I think this is a new agent that is clearly attacking the immune system.* ***And what you're seeing is an immunological disorder that's allowing a reactivation (of common viruses) very similar to what we saw in AIDS…. I point out that we're not just examining something that is fatigue – we're looking at something that gives immunological disorders****….The agent is kept so far underground by the immunological reaction, you will never find it".* **Several parameters of the**

disease "*tell us this is an autoimmune response to <u>something</u>"; autoimmune-like parameters included "enhanced T4 helper cell numbers (and) decrease in T8 cells, which is a model in the MRL mouse for autoimmunity".*

At that Conference, Drs Anthony Komaroff and Paul Cheney outlined some of the laboratory findings in people with CFIDS; these include lymphocytosis; low level ANA; monocytosis; anti-thyroid antibodies; elevated transaminases; circulating immune complexes; elevated B cell numbers; depressed levels of IgA; elevated T4/T8 ratio; NK cells not stimulated by IL-2, and elevated levels of cytokines – including IL-2 levels 50 times higher than normal (The CFIDS Chronicle, Spring 1989).

Dr Paul Cheney noted that 70% of ME/CFS patients tested had depressed levels of salivary IgA (SIgA), and that **ME/CFS patients with low SIgA levels tended to have high levels of insoluble circulating immune complexes**. **Microscopic analysis of tissues showed lymphocytic vasculitis (lymphoid infiltrates in the blood vessel wall) in 75% of patients tested.**

Reporting this medical conference, (Meeting Place issue 32), the Journal of the Australia and New Zealand ME Society (ANZMES) stated in its December 1989 issue: **"*The consensus of the conference was that CFIDS represents a growing pandemic of immune dysfunction"***.

1989

The Summer/Autumn (Fall) 1989 issue of The CFIDS Chronicle was a 180 page journal that reported on numerous conferences on (ME)CFS at which the immunological abnormalities were confirmed; it also addressed other areas of medical research into the disorder.

One book in particular was reviewed, this being *"The Body at War: The Miracle of the Immune System"* by Professor John M Dwyer (New York NAL Books, 1988; 253 pages). **The CFIDS Chronicle reviewer (Dr Dennis Jackson) noted that Dwyer, an Australian immunologist, condemned the "*intellectual arrogance*" of his fellow physicians who have continued to chase easy theories about the psychiatric origin of the disorder and that Dwyer declared: "*Unfortunately, continued widespread ignorance of the condition perpetuates psychological harassment for many….A genetic defect downgrading the efficacy of a response to infection should translate into an immunological defect, and this has now been established as fact.*** *The reproducible demonstration of T-cell abnormalities in patients with (ME)CFS is the reason we are discussing this disease in this book on the immune system….Patients with classical symptoms of (ME)CFS almost always have reduced numbers of immunoregulatory cells in their blood….So consistent are these abnormalities they allow us to make a positive diagnosis".*

1989

"Our investigations suggest that (ME)CFS is characterized by objective laboratory abnormalities. A more appropriate name for this syndrome would be chronic fatigue-immune dysfunction syndrome (CFIDS), since immune dysfunction appears to be the hallmark of the disease process" (Nancy Eby , Seymour Grufferman et al. In: Natural Killer Cells and Host Defense. Ed: Ades EW and Lopez C. 5th International Natural Killer Cell Workshop. Pub: Karger, Basel, 1989:141-145).

1989

*"**(ME)CFS has been associated with abnormal T cell function**. These patients have diminished phytohaemagglutinin-induced lymphocyte transformation and decreased synthesis of interleukin. We studied the display of CD3, CD5, CD2, CD4, CD8 and Leu-M3-defined antigen in peripheral blood mononuclear cells in (ME)CFS who fulfilled the (1988 Holmes et al) criteria. Patients had reduced expression of CD3. These data indicate that in (ME)CFS, some patients have T lymphocytes (CD2- and CD5- positive cells) without immunoreactive CD3"* (ML Subira et al. The Journal of Infectious Disease 1989:160:1:165-166).

1989

"Disordered immunity may be central to the pathogenesis of (ME)CFS. Reduced IgG levels were common (56% of patients), with the levels of serum IgG3 and IgG1 subclasses particularly affected. ***The finding of significantly increased numbers of peripheral blood mononuclear cells that express Class-II histocompatibility antigens (HLA-DR) in our patients implies immunological activation of these cells. Once activated, these cells may continue to produce cytokines which may mediate the symptoms of (ME)CFS***" (AR Lloyd et al. The Medical Journal of Australia 1989:151:122-124).

1989

"On medical history, the only clearly striking finding is a high frequency of atopic or allergic illness (in about 50 – 70%)…. ***On immunologic testing, we and others have found evidence of subtle and diffuse dysfunction****"* (AL Komaroff & D Goldenberg. J Rheumatol 1989:16:19:23-27).

1989

In 1989 The CFIDS Association of America published a "Brief Summary" by Anthony Komaroff from Harvard and Director of the Division of General Medicine and Primary Care at Brigham and Womens Hospital, Massachusetts: "***Considerable progress is being made in identifying various objective abnormalities, such as unusual immune system and nervous system findings. These advances are important (because) they identify measurable abnormalities that the patients cannot 'fake' ".***

1990

On 17th March 1990 Professor Peter Behan from Glasgow made a presentation to the Mid-Anglia branch of the ME Association in Cambridge; **he noted that 50% of ME patients cannot produce steroids in response to stimulus.**

1990

On 10th- 12th April 1990 the First World Symposium on ME/CFS was held at the University of Cambridge. Speakers presented evidence on acute, latent, persistent and reactive virus/host interaction; on cytopathological studies; on electron microscopy studies; on immunological abnormalities, genetics and autoimmunity; on interferons and their role in virus infections; on muscle studies of abnormal metabolic function; on cardiac disease in ME/CFS; on lesions in the brain and on paediatric ME/CFS. The predominant view was of a persistent or chronic viral infection which either gave rise to, or was the result of, a continuing abnormal immune response and abnormalities of the muscle and central nervous system. Evidence was presented of an infective vasculitis in ME/CFS. The Symposium brought together leading international researchers to review all aspects of ME/CFS. The proceedings were subsequently published as the 724 page seminal textbook on ME/CFS (The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome, edited by Drs Byron Hyde, Jay Goldstein and Jay Levy; The Nightingale Research Foundation, Ottawa, 1992).

1990

The 184-page issue of The Spring/Summer CFIDS Chronicle again covered (ME)CFS conferences and medical research; in addition it carried a section on "*Women's Issues"*, noting the immunological findings in women with endometriosis (often present in women with (ME)CFS), these being strikingly consistent with immunological findings in (ME)CFS in general. They also include the presence of anti-endometrial antibodies in peritoneal fluid and serum; deposits of complement C3 and C4 fractions in the endometrium, peritoneal fluid and sera, and increased number of activated macrophages in the peritoneal cavity.

1990

"The subgroup of patients with immunological abnormalities may have a prolonged illness" (DO Ho-Yen. JRCGP 1990:40:37-39).

1990

"In order to characterise in a comprehensive manner the status of laboratory markers associated with cellular immune function in

patients with this syndrome, patients with clinically defined (ME)CFS were studied. ***All the subjects were found to have multiple abnormalities in these markers****.* ***The pattern of immune marker abnormalities observed was compatible with a chronic viral reactivation syndrome. A substantial difference in the distribution of lymphocyte subsets of patients with (ME)CFS was found when compared with normal controls.*** *Lymphocyte proliferation after PHA and PWM stimulation was significantly decreased in patients (by 47% and 67% respectively) compared with normal controls.* ***Depression of cell-mediated immunity was noted in our study population, with over 80% of patients having values below the normal mean****. The present report confirms that a qualitative defect is present in these patients' NK cells (which) might represent cellular exhaustion as a consequence of persistent viral stimulus. Results from the present study indicate that there is an elevation in activated T cells.* ***A strikingly similar elevation in CD2$^+$ CDw26$^+$ cells has been reported in patients with multiple sclerosis. In summary, the results of the present study suggest that (ME)CFS is a form of acquired immunodeficiency. This deficiency of cellular immune function was present in all the subjects we studied"*** (Nancy G Klimas et al. Journal of Clinical Microbiology 1990:28:6:1403-1410).

1990

"*It is also clear that acquisition of T cell deficiency, particularly of the CD8 subset, can itself impair immune regulation and predispose to atopy not previously experienced by the patient. Three of the criteria are sufficiently frequent to suggest they should become part of the routine screening of such patients, and these are a subnormal level of CD8 lymphoctyes, a raised serum IgE level and a positive VP1 antigen….* ***In the present ME study, patients show a 40% incidence of both clinical and laboratory evidence of atopy….*** *It has been shown that T cell deficiency, particularly of the suppressor subset, can predispose to atopy, which can indeed be acquired by patients without a genetic family history.* ***We have undertaken extensive T cell subset measurements in normal subjects subjected to psychological stress and would point out in none of these did we see CD8 levels as low as in some 40% of our ME patients****"* (JR Hobbs, JA Mowbray et al. Protides of Biological Fluids 1990:36:391-398).

1990

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

- Dr Irina Rozovsky (speaking on "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 receptors 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 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 entero, coxsackie, 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".

- Professor Nancy Klimas in her presentation entitled "Immunological markers in (ME)CFS" 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".***

- 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".***

1991

The Spring 1991 (131-page) issue of The CFIDS Chronicle reported in full on the Charlotte, North Carolina, Conference, noting that Professor Nancy Klimas ***"unequivocally stated that all of her (ME)CFS patients had predictable laboratory abnormalities and that (ME)CFS is a form of acquired immunodeficiency".***

1991

In a Statement on 16th April 1991 by Dr Elaine DeFreitas and Dr Hilary Koprowski regarding CFIDS/ME to the US House of Representatives Committee on Energy and Commerce Subcommittee on Health and the Environment, Washington DC, Dr DeFreitas spoke out with a very strong voice: *"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".***

1991

"*Compared with controls, (ME)CFS patients showed an increase in CD38 and HLA-DR expression.* ***These data point to a high probability (90%) of having active (ME)CFS if an individual has two or more of the CD8 cell subset alterations. Laboratory findings among (ME)CFS patients have shown low level autoantibodies, which may reflect an underlying autoimmune disorder****. A persistent hyperimmune response of the remaining CD8 cells might lead to an outpouring of cellular products and cytokines (e.g. interferon, tumour necrosis factor, interleukin-1) that are characteristically associated with myalgia, fatigue, (and) neurological signs and symptoms associated with acute viral infections.* ***Unless the immune system is brought back into balance, this chronic activation affects the individual further and might eventually lead to other clinical illnesses****"* (Alan L Landay et al. Lancet 1991:338:707-712).

1991

"Despite the broad divergence of opinion in the medical community, there is little doubt that classic allergy and atopy are inexplicably prevalent in (ME)CFS. In a recent study, a high proportion (50%) of patients were found to be reactive to a variety of inhalant or food allergens when inoculated epicutaneously in the classic manner. ***Certainly patients with (ME)CFS differ immunologically from their healthy counterparts and it is this observation, more than any other today, that is evoked in support of the organic hypothesis of disease causation***" (Stephen E Straus. Reviews of Infectious Diseases 1991:13: Suppl 1: S2-S7).

1991

"*Various abnormalities revealed by laboratory studies have been reported in adults with (ME)CFS.* ***Those most consistently reported include depressed natural killer cell function and reduced numbers of natural killer cells; low levels of circulating immune complexes; low levels of several autoantibodies, particularly antinuclear and antithyroid antibodies; altered levels of immunoglobulins (and) abnormalities in number and function of lymphocytes****"* (Dedra Buchwald and Anthony Komaroff et al; Reviews of Infectious Diseases 1991:13 (Suppl 1): S12- S28).

1991

"Our investigations have…produced evidence of …a decrease in CD8 suppressor cells with resulting elevation of the ratio of CD4 to CD8 cells*"* (Sandra Daugherty, Daniel Peterson et al. Reviews in Infectious Diseases 1991:13 (Suppl 1):S39-S44).

1991

"Preferably, patients with (ME)CFS who have such abnormalities might be considered a subset of the larger group: i.e. persons with (ME)CFS who have immune dysfunction*"* (Gary P Holmes. Reviews of Infectious Diseases 1991:13:1:S53-S55).

1991

Referring to the seminal work of Dr Elaine DeFreitas, the Autumn (Fall) 1991 issue of The CFIDS Chronicle heralded "*Convincing Evidence of Retroviral Infection and Immune Activation Found in CFIDS Patients"*; other topics included a review of an article published in The Lancet (1991:338:8769:707-712) by Drs Jay Levy, Alan Landay, Carol Jessop and Evelyne Lennette from the University of California School of Medicine entitled "*Immune Activation in CFS"*. The review noted: "*Drs Levy, Landay, Jessop and Lennette reported the results of their study which further explored findings that (ME)CFS may be due to one or more immune disorders that have resulted from exposure to an infectious agent….Flow cytometry studies, white blood cell counts, differential counts and viral serology studies were performed. Analysis of all clinical data enabled the research team to group the patients according to symptoms number and severity.* ***Group A was comprised of 67 patients whose illness was so severe that they had less than 25% of their normal daily activity and also had multiple symptoms….The immunophenotypic data presented here indicate that many individuals with symptoms of (ME)CFS have CD8 cell immune activation….Most noteworthy is the statistical evidence that an individual with two or more of the CD8 cell subset alterations (increased CD11b-, CD38, and HLA-DR)***

has a high probability (90%) of having active (ME)CFS. These findings are consistent with chronic stimulation of the immune system*, perhaps by a virus".*

1992

On 20th December 1991 the Principal Investigator of (ME)CFIDS studies at the US Centres for Disease Control (CDC) , Dr Walter Gunn, had announced to The CFIDS Association: "***Our Surveillance Study does not support the notion that (ME)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****"* (The CFIDS Chronicle, February 1992).

1992

A major study looking at neurological, immunological and virological aspects in 259 (ME)CFS patients found that neurological symptoms, MRI findings and lymphocyte phenotyping studies suggest that patients ***"may have been experiencing a chronic, immunologically mediated inflammatory process of the central nervous system****"* and that ***" We think that this is probably a heterogeneous illness that can be triggered by different environmental factors (including stress, toxins and infectious agents), all of which can lead to immune dysfunction and the consequent reactivation of latent viruses****"* (Dedra Buchwald, Paul Cheney, Daniel Peterson, Robert C Gallo, Anthony Komaroff et al. Ann Int Med 1992:116:2:103-113).

1992

"It is known that such patients are remarkably likely to have a history of atopy pre-dating the onset of chronic fatigue syndrome (50-83%). ***Patients may have an immune system that responds over-emphatically to environmental or internal stimuli…aspects of the immune reaction may not be stoppable even after an insult is over"*** (WK Cho & GH Stollerman. Hospital Practice 1992:221-245).

1992

"Patients with chronic fatigue syndrome are reported to have a higher incidence of allergic conditions. Indeed, it has been speculated that heightened allergic responsiveness may be a risk factor for the development of the syndrome. ***In particular, the diverse clinical and immunological features have been argued to reflect an ongoing state of immune activation****"* (MA Demitrack, Stephen E Straus et al. Biol Psychiatry 1992:32:1065-1077).

1992

In September 1992 The CFIDS Association produced another issue of "A Physicians' Forum" (entitled "CFIDS: The Diagnosis of a Distinct Illness"), with contributions from world-class experts including Professors/Drs David Bell, Leonard Calabrese, Paul Cheney, Jay Goldstein, James Jones, Nancy Klimas, Anthony Komaroff, Charles Lapp, Benjamin Natelson, and Daniel Peterson.

Dr David Bell said: "*Differential diagnosis includes rheumatoid arthritis, lupus erythematosus, Lyme disease, multiple sclerosis, sarcoidosis, hepatitis B, polymyalgia rheumatica, human immunodeficiency virus infection and malignant disease….****Numerous immunologic abnormalities have been described in patients with (ME)CFS….Decreased natural killer cell function is perhaps the most reproducible immunologic abnormality".***

Dr Leonard Calabrese (Head of the Clinical Immunology Section in the Department of Rheumatic and Immunologic Disease at the Cleveland Clinic Foundation) said: "***Growing experimental evidence suggests that a portion of patients with (ME)CFS have both qualitative and quantitative immunologic abnormalities. When the immune system of patients with (ME)CFS is challenged, the response is quantitavely abnormal. Mononuclear cells from patients with (ME)CFS proliferate at half the expected rate following challenge with phytohaemagglutinin and pokeweed mitogen….A deficiency in certain natural killer cells has been proposed to explain many of these abnormalities****".*

Drs Paul Cheney and Charles Lapp said: "***Immunologic tests have been frequently applied to patients with (ME)CFS in part because they are frequently abnormal and in part because the signs and symptoms of (ME)CFS can be explained as a consequence of immunologic dysfunction****….**We propose a set of tests that look for evidence of T-cell activation along with discrete immune defects….Immune tests become more valuable when used as an array or set of tests used to determine a pattern of immune dysfunction*"

Dr Jay Goldstein noted that ***"The sed rate*** (erythrocyte sedimentation rate or ESR) ***is often very low"*** (an important observation because many physicians dismiss ME/CFS as an infectious disease unless there is a high ESR, but if inflammatory processes are activated in other ways, the ESR can remain normal or low, which does not exclude an inflammatory illness); ***"Immune complexes and positive anti-nuclear antibodies are encountered very frequently….Elevated levels of various cytokines and their receptors are often seen".***

Professor Nancy Klimas said: "*Our group in Miami has been actively working to better understand CFIDS since 1985.* ***This work has focused on the immunologic abnormalities seen in the majority of patients (and) 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 evaluated….We have found the immune evaluation to be … important, as it not only helps classify the patients, but also helps to direct the care of the patient….Such an evaluation must touch on three points: (1) level of T cell activation….while there are many markers of T cell activation…the most sensitive in CFIDS is CD3+CD26+ phenotype by flow cytometry, the T cell expressing transferrin receptor. In 'normals', about 18 percent of circulating T cells express this activation marker, while CFIDS patients show double to triple these levels of activation****. Other phenotypic markers help to fill out the picture. CD8+DR, or activated cytotoxic cells, are elevated in the majority of patients with recent exacerbations but seem to normalise during healthier times. (2) diminished cell function….**CFIDS patients have diminished T and B cell function in response to cell activators (mitogens) in culture****. The most sensitive is diminished response to pokeweed mitogen (PWM), which reflects poor T and B cell interaction.* ***Even more remarkable is the very poor ability of NK cells to kill virally infected target cells in culture…People with CFIDS often have very diminished NK cell function….While we routinely look at both mitogen response and NK cytotoxicity, I believe assessing NK cytotoxicity is more important. We also routinely assess B cell function by looking at immunoglobulin production.*** *Basically this is accomplished by looking at total immunoglobulins (IgG, IgA, IgM), at IgG subclasses (IgG. IgG2, IgG3, IgG4)….(3) evidence of viral reactivation.* ***Serology for common reactivation viruses…adds further evidence that the immune dysfunction now quantified is of a serious enough nature to cause secondary viral reactivation****….**The Miami group's enthusiasm and excitement are based on …our understanding of the underlying immune defects are finally sharply focused.*** *This clear understanding of the immune disorder is driving new therapeutic approaches".*

Professor Anthony Komaroff said: "***Our studies indicate that two additional tests are elevated more often in patients with CFIDS: immune complexes and immunoglobulin*** *G (IgG)".*

Dr Benjamin Natelson (Professor of Neurosciences at the University of Medicine and Dentistry, New Jersey) said: ***"The major lab tests I check are those indexing immunological dysfunction. I do a standard 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 (payment)".

1992

On 2nd – 4th October 1992 the First Biennial International Research conference on (ME)CFS was held at Albany, New York. It was reported in the CFIDS Chronicle, Summer 1993; pages 64 – 72.

Professor Nancy Klimas et al considered the possibility of a genetic predisposition and by using HLA phenotyping they were able to provide substantial support for it; DQ1 and DR4 appear to be present in a large percentage of the (ME)CFS population and Klimas et al were investigating the possibility that HLA DR4 and DQ1 may be genetic markers for (ME)CFIDS. **Whilst HLA DR4 and DQ1 represent less than 5% of the general population, they were present in 93% of the (ME)CFIDS population.** Charles Lapp (Associate Professor of Family Medicine, Duke University) commented "*This study establishes that two gene markers occur frequently in (ME)CFIDS but not in the general population".*

Drs David Bell and Paul Cheney discussed the T4/T8 ratio in (ME)CFIDS, noting that **low CD8 counts are more likely to occur in (ME)CFIDS than low CD4 counts, so the ratio is likely to be high in this disorder** (i.e. facilitating an allergic or hyperimmune response)**.**

Dr Emmanuel Ojo-Amaize reported on the association between decreased NK cell activity and the severity of (ME)CFS; **the results confirmed and extended previous reports demonstrating that a pronounced and consistent immunological abnormality detected in (ME)CFS patient is low NK cell cytotoxicity.**

1993

A press release of 5th February 1993 from the NIAID stated: "***Researchers at the National Institute of Allergy and Infectious Diseases (NIAID) report finding subtle immune abnormalities in people with chronic fatigue syndrome (CFS) that ultimately may explain why they develop painful muscles and joints, and tender lymph nodes and other symptoms associated with the illness….When the researchers compared blood samples from…healthy volunteers with those from…CFS patients, they found several immune differences. These findings confirm and add new information to other immunological studies of CFS. Most notably, the CFS patients had significant differences in the number and character of one type of immune cell – T cells that carry helper molecules, called CD4, on their surfaces. These cells, known as CD4+T cells, orchestrate the immune response****….(Dr Stephen Straus said) '**More CD4+T cells appear to change location, shifting from the blood into the tissues. These tissue-based cells escape detection by research blood tests'….In the tissues, CD4+T cells release molecules that help regulate the immune response. These molecules can cause mild inflammation and pain**. 'The same process causes pain in the intestines of people with inflammatory bowel disease' says Dr (Warren) Strober, another member of the team who is an immunologist and expert in inflammatory bowel disease….The NIAID study will continue for several years….the data collected will be analysed to determine if these or other immunological differences found vary with time or correlate with symptoms severity or recovery"* (The CFIDS Chronicle, Winter 1992-1993).

1993

On 8th February 1993 The CFIDS Association of America issued a press release: "***Government Finally Confirms Private Sector Research: Immune Abnormalities Found in Chronic Fatigue Syndrome. Federal scientists at the National Institute of Allergy and Infectious Diseases have published a study in the January 1993 issue of the Journal of Clinical Immunology reporting findings of immune abnormalities in (ME)CFS patients which confirms earlier studies performed by private sector researchers….It is the first acknowledgement by federal scientists that the 'ID' in CFIDS is indeed real. Over the past several years private sector researchers have been publishing similar studies, reporting various immune abnormalities in CFIDS patients****".*

1993

At the 1993 Los Angeles Conference (7th - 9th May) on (ME)CFS, evidence was presented by Professor Nancy Klimas from the University of Miami that she and her team have been able to accurately predict 88% of (ME)CFS patients with a mathematical model of immunological parameters. This model combines levels of activated T cells and CD4 inducers of cytotoxic T cells with NK cell count and function: "***In a normal population, 20% of lymphocytes are active at any***

given time. 'In (ME)CFS, up to 80% 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".

At the same conference, Dr Catherine Rivier from the Salk Institute in La Jolla, California, said: "***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. 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***" (CFIDS Chronicle: Summer 1993).

1993

*"**Using the immunophenotypic data presented, we were able to demonstrate that almost 50% of (ME)CFS patients, especially those with severe symptoms, showed signs of $CD8^+$ cell activation and an abnormal suppressor/cytotoxic $CD8^+$ cell ratio. Our observations strongly suggest that a large population of (ME)CFS patients have immunologic disorders and that their symptoms could be explained by a chronic immune activation state (and) that (ME)CFS represents a type of autoimmune disease in which a chronically activated immune system reacts against the host**. The 3:1 female/male ratio would not be unexpected: autoimmune syndromes are more common in women. **Because of the autoreactive nature of this condition, it might also lead to other immune disorders, such as well-recognised autoimmune diseases and multiple sclerosis"*** (Jay A Levy et al. Contemp Issues Infec Dis 1993:10:127-146).

1993

*"On past medical history, the only clearly striking finding in our studies is a high frequency of atopic or allergic illness (in approximately 50 – 80%, in contrast to a background prevalence of about 10% in the population at large)…..**Immunological studies suggest that in CFS, the immune system is in a state of chronic activation**"* (AL Komaroff. Ciba Foundation Symposium 173: Chronic Fatigue Syndrome. John Wiley, Chichester 1993:43-61).

1993

"***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"*** (Dr James McCoy from Louisiana; The CFIDS Chronicle Physicians' Forum, Autumn (Fall) 1993).

Two further 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***".

1993

"What is ME? ME is a potentially severe and chronic condition affecting the immune and central nervous system" (Perspectives -- the magazine of the UK ME Association, September 1993, page 10).

1993

In September 1993 meetings took place at the CDC to review the CFS case definition. A common theme articulated was the urgent need to change the name: "***Dr Nancy Klimas (a noted CFIDS immunologist at the University of Miami)***

supported a formal change to 'chronic fatigue and immune dysfunction syndrome' in recognition of the various immune abnormalities documented by private and public-sector researchers….Dr Klimas presented Dr Reeves with a notebook filled with medical articles on the immune abnormalities found in CFIDS in defence of this recommendation*".*

During those meetings, Dr Phillip Peterson acknowledged the immune system abnormalities and the adequacy of evidence to support immunotherapy, stating that **he had found no other disease with such global immune disturbance** (The CFIDS Chronicle, November 1993 and Winter [January] 1994).

1994

An International Meeting on (ME) Chronic Fatigue Syndrome was held in Dublin on 18th-20th May 1994 under the auspices of the World Federation of Neurology.

Professor Dr Rainer Ihle from Germany said that data on 375 (ME)CFS patients demonstrated various immunological changes and autoantibodies (especially antinuclear antibody and microsomal thyroid antibodies) in an abnormally large proportion of 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 (ME)CFS has now been demonstrated"***).

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. 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.**

1994

"The up-regulated 2-5A pathway in (ME)CFS is consistent with an activated immune state and a role for persistent viral infection in the pathogenesis of (ME)CFS. The object of this study was to measure key parameters of the 2-5A synthetase/RNase-L antiviral pathway in order to evaluate possible viral involvement in (ME)CFS. The data presented suggest that 2-5A synthetase/RNase L pathway is an important biochemical indicator of the anti-viral state in (ME)CFS. ***Evidence that this pathway is activated in (ME)CFS was identified in this subset of severely disabled individuals as related to virological and immunologic status. This pathway phenotype could result from chronic over-stimulation due to chronic viral reactivation****"* (RJ Suhadolnik et al. Clin Inf Dis 1994:18(Suppl 1):S96-S104).

1994

"*Controlled studies of T cells in patients with (ME)CFS have (shown that) the three most prominent and apparently reproducible findings for (ME)CFS patients are as follows (1) Impaired lymphocyte proliferation in response to stimulation…has been repeatedly documented and also has been shown to be dissociated from the potential effect of concurrent mood disturbance on this response. (2) …several investigators have reported increased numbers of peripheral blood lymphocytes bearing activation markers (such as HLA-DR and interleukin-2R) in these patients. (3) Impaired cell-mediated immune function in vivo is suggested by reports of an increased number of reduced or absent DTH* (delayed-type hypersensitivity) *skin testing responses in patients with (ME)CFS"* (AR Lloyd. Clin Inf Dis 1994:18: (Suppl 1): S134-5).

1994

"Compared with those of healthy individuals, patients' CD8+ T cells expressed reduced levels of CD11b and expressed the activation markers CD38 and HLA-DR at elevated levels…These findings indicate expansion of a population of activated CD8+ cytotoxic T lymphocytes. A marked decrease in NK cell activity was found in almost all patients with (ME)CFS, as compared with that in healthy controls…The results of this study suggest that immune cell phenotype changes and NK cell

*dysfunction are common manifestations of (ME)CFS…**Because several immune abnormalities have been associated with this syndrome, the disorder has also been termed chronic fatigue immune dysfunction syndrome…A characteristic of (ME)CFS is a disordered immune system characterised by abnormal cell-surface marker expression and cellular immune function. …In patients manifesting incapacitating symptoms, the CD8+11b+ population is considerably reduced, and this reaches statistical significance….in agreement with the findings of other investigators, a decrease in NK cell-mediated lysis appears to be directly related to symptoms observed in (ME)CFS…The loss of these regulatory cells may allow for enhanced activation of other CD8+ lymphocytes such as the cytotoxic cells. Activated cells can over-produce cytokines that cause the symptoms characteristic of (ME)CFS"*
(Edward Barker, Alan L Landay, Jay A Levy et al. Clin Inf Dis 1994:18: (Suppl 1): S136-41).

1994

"Overall, 60% of patients had elevated levels of one or more of the nine soluble immune mediators tested…In patients with (ME)CFS – but not in controls – serum levels of TNF-alpha, IL-1 alpha, IL-4, and sIL-2R correlated significantly with one another and (in the 10 cases analysed) with relative amounts (as compared to beta-globin or beta-actin) of the only mRNAs detectable by reverse transcriptase-coupled polymerase chain reaction in peripheral blood mononuclear cells….These findings point to polycellular activation…. The immune system is a readily accessible, sensitive indicator of environmental or internal changes, and studies conducted by different groups over the past few years have provided valuable evidence for changes in immune status among individuals with (ME)CFS….** To gain insight into the nosology and aetiology of (ME)CFS, we assessed patterns of soluble immune mediator expression at the protein and mRNA levels in individuals with (ME)CFS….**The data presented in this report are consistent with previous evidence of immune dysregulation among patients with (ME)CFS and point to a dysregulation of TNF** (tumour necrosis factor) **expression as a distinctive feature of this condition….Imbalances in TNF and associated changes in levels of other cytokines may underlie many of the characteristic features of (ME)CFS…. In addition, TNF-α can have deleterious effects on the central nervous system" (Roberto Patarca, Nancy G Klimas et al. Clin Inf Dis 1994:18: (Suppl 1):S147-153).

Tumour necrosis factor is a cytokine involved in systemic inflammation. Its primary role is in the regulation of immune cells. Increased TNF causes apoptosis, inflammation and tumorigenesis.

1994

***"The chronic fatigue immune dysfunction syndrome (CFIDS) is a major subgroup of the chronic fatigue syndrome (CFS)…. We and other investigators have reported a strong association between immune dysfunction and a serological viral activation pattern among patients in this group. This finding appeared similar to that for a variety of 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. **We thus elected to examine a cohort of patients with CFIDS, with use of HLA-DR/DQ typing**…. **A significant association between CFIDS and the presence of HLA-DQ3 was noted**…. The association with HLA-DQ3 could represent an additive effect for patients who also have HLA-DR4 and/or HLA-DR5…. The results presented are intriguing. DQ3… was significantly more prevalent in patients than the …control groups. It is possible that DR4 and DR5 are also associated with an increased risk of developing CFIDS…. **These findings strongly suggest that further evaluation of persons with CFIDS, including an investigation of an HLA Class I linkage dysequilibrium…are warranted**….The data presented herein suggest that CFIDS, together with a variety of immune-mediated diseases…may share similar sequences of pathogenic mechanisms….It may be speculated that in a subpopulation (of CFIDS), a genetic predisposition may be triggered immunologically by any number of potential stimuli, **resulting in a state of chronic immune dysequilibrium**. This model could easily explain the recent findings with regard to acute viral infections, chronic active viral infection (and) allergies"* (RH Keller, N Klimas, MA Fletcher et al. Clin Inf Dis 1994:18: (Suppl 1): S154-156).

1994

"These data suggest a correlation between low levels of NK cell activity and severity of CFIDS…. Compromised or absent natural immunity is associated with…acute and chronic viral infections such as AIDS, CFIDS… and various immunodeficiency syndromes. Our results confirm and extend previous reports that low NK cell cytotoxicity is a pronounced immunologic abnormality found in some patients with (ME)CFS… The fact that NK cell activity decreases with increased severity and duration of certain clinical variables suggests that measurement of NK cell function could be useful for stratification of patients and possibly for monitoring therapy for and/or the progression of CFIDS" (EA Ojo-Amaize et al. Clin Inf Dis 1994:18: (Suppl 1):S157-159).

1994

"In summary, recent data, including findings presented in this supplement, have continued to support the possibility that immunologic factors are important in the development of (ME)CFS. Several potentially important clues to the nature of the immunologic disturbance are available. The time is ripe for more sophisticated immunologioc hypotheses for the pathogenesis of (ME)CFS) to be developed and tested" (Andrew R Lloyd and Nancy Klimas. Clin Inf Dis 1994:18: (Suppl 1):S160-161).

1994

*"**Abnormalities of immune function, hypothalamic and pituitary function, neurotransmitter regulation and cerebral perfusion have been found in patients with (ME/CFS). Recent research has yielded remarkable data.** The symptoms of (ME)CFS have long been viewed as a neurologic pattern, as confirmed by other names such as myalgic encephalomyelitis. A link is being forged between the symptoms pattern of (ME)CFS and objective evidence of central nervous system dysfunction. **The view that (ME)CFS is a primary emotional illness has been undermined by recent research**"* (David S Bell. Postgraduate Medicine 1994:98:6:73-81).

1994

On 13th September 1994 the Report of the UK National Task Force on CFS/PVFS/ME was published; it was an initiative of the charity Westcare (no longer in existence) and was supported by the Department of Health and the Wellcome Trust. The section on immunology states: "*Many groups have suggested that an immunological disturbance could account for the clinical features of the chronic fatigue syndrome (and) many have described abnormalities of immune function….NK cells have been studied particularly intensively in patients with (ME)CFS**….Two main patterns of immunological abnormality have emerged from detailed studies of patients…the first is immunodepression and the second is activation of the immune system….Reduced NK cell function has been consistently reported**….Strict criteria for diagnosing (ME)CFS have improved the correlation between the results of the immunological investigations and the clinical features of the patients studied….**Perhaps the principal practical value of immunological tests, as currently performed, is to give additional evidence for an organic component**".*

1994

The Autumn (Fall) 1994 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".***

1994

The Second Biennial International Clinical and Research 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.

Dr Seymour Grufferman (Pittsburgh Cancer Institute) described an (ME)CFS outbreak in the North Carolina Symphony Orchestra; the cases demonstrated persistent decreases in NK cell cytotoxicity and CD56 and CD16 cell populations and elevations in the CD4 population. These alterations were not seen in control subjects and could not be attributed to stress or gender. **He concluded that (ME)CFS cases have a broad dysregulation of the immune system that persists over time**.

Dr Richard Lanham (State University of New York) presented **a study of autoimmune disease in the families of patients with (ME)CFS and found more autoimmune disorders in their families**, including thyroiditis, lupus, rheumatoid arthritis and allergy, causing him to consider that (ME)CFS patients may have an inherited genetic predisposition to immunological diseases such as (ME)CFS.

Dr Joseph Cannon (Pennsylvania State University) provided historical and scientific evidence that females are more resistant to infection than males because of upregulation of the immune system. However it is because of this upregulation that women are more susceptible to autoimmune diseases.

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 James Jones (National Jewish Centre for Immunology, Denver), in the "Ask The Experts" session, said: "*There is literature that suggests that allergic patients, when they get sick, have more symptoms and are sicker longer than other individuals…A number of my patients with allergies have seen increases in their systemic illness when treated with immunotherapy".*

Dr Adrienne Bennett (from Brigham & Women's Hospital, Boston) measured transforming growth factor beta (TGFβ) 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 Lawrence Borish (National Jewish Centre for Immunology, Denver) measured TNF-α, IL-1, IL-6 and IL-10 (all associated with lethargy and inflammation); they found that TNF-α and INF-α (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-α, 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 Irving Salit (Toronto General Hospital) found that the percentage of CD4 (T-helper cells) was increased in ME/CFS patients (a finding that is seen in people with allergies) compared with chronically fatigued controls who did not meet the CDC case definition for ME/CFS. **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 (Miami) **described three groups of ME/CFS patients based on patterns of cytokine dysregulation: (1) dysregulation of TNF-α/β expression in association with changes in serum levels of IL-1α, IL-4, (soluble) IL-2R and IL-1 receptor agonist; peripheral blood mononuclear cell-associated expression of IL-1β, IL-6 and TNF-β messenger RNA, and T-cell activation; (2) inter-related and dsyregulated expression of soluble TNF receptor types 1, (s)IL-6R and β2-microglobulin, and significantly decreased lympho-proliferative activity; (3) significantly decreased NK cell cytotoxic activity.**

Dr Kenny De Meirleir (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.**

1995

At the ACMA (Australian Complementary Medicine Association) National Consensus Conference held on 18th and 19th February 1995 in Sydney, Dr Paul Cheney presented his protocol for immunological testing: "*Low level ANAs that fluctuate positive/negative are very common; various dysgammaglobulinaemias, including high IgG levels, low IgG levels and subclass deficiencies, are fairly common, and C1Q immune complexes can be common; (using) two colour flow cytometry looking at various immune activation markers, the one that we found the most sensitive is the CD3 CD26 marker for immune activation:* ***a very interesting one has been the CD4/CD8 ratio – in the Lake Tahoe patients we see extraordinary elevations with this ratio, well above 10, we see 10 – 12 – 14 as the value of this ratio (due to both CD8 depletion and CD4 expansion****). We've also seen a subset of patients, about 15%, with low CD4 counts….(With) serum and then cell-associated alpha interferon levels, we're getting 60% on serum and on cell associated testing, 90% positivity…(The) IL-2 receptor can mark immune activation in the various immune function tests with respect to NK function. I've learnt that it's important to assess the NK killing per NK cell and not just the gross kill….(We also use) various mitogen stimulation tests".*

1995

"One rationale for the immunological approach stems from the experience accumulated with similar syndromes such as autoimmune and environmentally-triggered diseases. (ME)CFS may be associated with certain HLA Class II antigens, as are some forms of environmental disease. These observations underscore the distinction between (ME)CFS and psychiatric maladies. Viruses are frequently reactivated in association with immune system dysregulation in (ME)CFS and may contribute to symptomatology" (Roberto Patarca. JCFS 1995:vol I:3/4:195-202).

1995

On 23rd September 1995 350 people gathered in Charlotte, North Carolina, to attend a CFIDS Association conference at which esteemed researchers and clinicians from across America presented current information about (ME)CFIDS. It was reported in The CFIDS Chronicle, Autumn (Fall) 1995.

Professor Nancy Klimas presented her University of Miami research group's model of the proposed mechanism of (ME)CFDS, explaining that in this preliminary model, **her group found genetic similarities very similar to those found in autoimmune diseases such as lupus erythematosus. She said that the typical CFIDS immune system is *"noisy"* or over-active, churning out chemicals in a chronic war against a real or perceived invader. In healthy people only 20% of the immune system cells (cytokines, interleukins and interferons) are activated at any one time, but in (ME)CFIDS, 60% of the cells are activated. For chronic immune activation to occur, something must be perpetuating the illness, which may include latent viral infections such as HHV-6, allergies and HPA axis dysregulation.**

Dr Jay Levy explained that once the immune system is activated, if the cells designed to quieten the immune response were not available, a disease such as (ME)CFIDS might be the result. **Based on advanced immunological testing, Levy et al found that the immune system's NK and suppressor cells are not working in (ME)CFIDS patients and he regularly screens (ME)CFIDS patients for this potential marker.**

1995

The First World Congress on Chronic Fatigue Syndrome and Related Disorders, organised by The Department of Human Physiology at the Vrije Universiteit, Brussels, with The Ramsay Society, The World Federation of Neurology and The

University of Glasgow, was held at The European Conference Centre, Brussels, on 9th – 11th November 1995.

Session V was on the Immunology of (ME)CFS and was chaired by Professor Nancy Klimas and by Professor Umberto Tirelli.

Professor Nancy Klimas (Miami) spoke on "*The Immunopathogenesis of (ME)CFS" -- "(ME)CFS is characterised by a state of chronic immune activation and dysfunction, an observation confirmed by investigators in the US, Australia, Italy, Germany and the UK. The Miami group has longitudinal data suggesting patterns of immune dysfunction that correlate with the relapse/remitting nature of the illness. Specific patterns of soluble mediators suggest a key role for TNF alpha, and TNF receptor.* ***Miami and other groups have shown that the degree of cellular dysfunction correlates with illness severity****"* (Conference Proceedings, page 28).

Professor Umberto Tirelli (Director, Department of Medical Oncology, National Cancer Institute, Aviano, Italy) spoke on "*Immunologic abnormalities in (ME)CFS" – "****Immunological abnormalities so far associated with (ME)CFS include a decreased number and function of NK cells, the presence of chronically activated circulating T cells, abnormal distribution of T cell subsets, monocyte alterations, changes in B cells subsets, and abnormalities in cytokine serum levels or in vitro response of lymphocytes to mitogenic stimulation….Overall, (ME)CFS appears most likely to be a chronic disorder of the immune system probably caused by an infectious agent…with a chronic immune activation, in particular of cytokines and T lymphocytes****"* (Conference Proceedings, page 29).

Dr Arnold Hilgers (Dusseldorf, Germany) spoke on ***"CFS: Evaluation of a 30-Criteria Score and Correlation with Immune Activation" – "Correlation between this 30-criteria score and immunological parameters could be evaluated in 472 out of the 505 patients. Significant positive correlation to the 30-criteria score was found in: CD8+ T-lymphocytes, DR+ T-lymphocytes, gamma globulin, IgM, IgG, and the number and types of autoantibodies (mainly ANA, ACA, thyroidal and parital antibodies)….In more and more larger groups of patients with (ME)CFS…we often see clinical signs (and) specially a high prevalence of…prolonged inflammatory processes.*** *Together with other results published by us and other investigators the data further confirm the hypothesis that a reduced or unstable immune control or delayed immune reaction to persisting viruses or bacterial intracellular pathogens can – triggered by common infections or other environmental factors – lead to a* ***chronic neuro-immune activation state and autoimmune disorders****"* (Conference Proceedings page 30).

In Poster Session I on 10th November 1995, Drs Mary Ann Fletcher, Roberto Patarca and Nancy Klimas posted on "*Soluble receptors and chronic fatigue syndrome*", whilst L Habets, H Knechten and P Braun (Aachen, Germany) posted on "*Patterns of immune dysfunction in patients with CFS".*

In Poster Session II on 11th November 1995, C Demanet, E Joos, P de Becker, B Fischler and Kenny De Meirleir posted on "*Evidence for immune activation in a subset of chronic fatigue syndrome patients"*, whilst HJ Whelton, TJ Smith and EJ Fitzgibbon posted on "*HLA-DR class II antigens and postviral fatigue syndrome".*

1995

On 18th November 1995 Professor Anthony Komaroff, Director and Professor of Medicine at Harvard Medical School, addressed an audience in London. For the benefit of the UK audience, he referred throughout to CFS as ME. With reference to the immune disturbance in ME/CFS, he said: ***"Now let's turn to other objective laboratory studies. This is a paper we published three months ago, in which we basically summarised 10 years of laboratory studies, conducted on over 7,000 patients with ME from two different geographic areas in the States, who over 10 years have had 18,000 lab tests****. These patients were compared with healthy people of the same age and sex. All blood samples were tested by technicians who did not know if a sample came from a healthy or an ME person.* ***We found very striking increased frequencies of abnormalities: immune complexes were found nearly 27 times more often in ME patients than in healthy people. Elevated levels of immunoglobulin G were found nearly nine times more often in the ME patients. Unusually shaped white blood cells were found***

eleven times more often, also several other abnormalities. So these tests are saying there is, in the true ME patient, an activation of the immune system….There is more evidence in the literature that the immune system in ME is chronically turned on. I think that the body of evidence overwhelmingly says there is a chronic state of immune activation in these patients – as if they are fighting against something" (Perspectives, March 1996).

1996

"Many CFS patients have a history of allergies years before the onset of the syndrome…Sometimes patients report a worsening of allergic symptoms or the onset of new allergies after becoming ill with CFS…..Allergies are common in people with CFS….(there is a) high prevalence of allergies in the CFS population….many patients are extremely sensitive to drugs" Chronic Fatigue Syndrome. Information for Physicians. Issued in September 1996 by The National Institute of Allergy and Infectious Disease; National Institutes of Health (NIH), US Department of Health and Human Services.

1996

An important paper from Konstantinov and Tan et al demonstrated the occurrence of autoantibodies to a conserved intracellular protein (lamin B1), **which provides laboratory evidence for an autoimmune component in ME/CFS**. The authors found that 52% of patients with ME/CFS develop autoantibodies to components of the nuclear envelope (NE), mainly nuclear lamins, suggesting that in addition to the other documented disturbances of the immune system, **humoral autoimmunity against polypeptides of the NE is a prominent immune derangement in ME/CFS. 67% of ME/CFS patients were positive for NE reactivity compared with 10% of normal controls. Autoantibodies to NE proteins are relatively infrequent and most fall into the category of an unusual connective tissue disease characterised by brain or skin vasculitis.** The authors concluded that such activation ***"could be the result of various triggering agents, such as infections or environmental toxins. Future work should be directed at a better understanding of the autoimmune response of (ME)CFS patients to other NE antigens"*** (K Konstantinov et al. J Clin Invest 1996:98:8:1888-1896).

1996

As presented at the First World Congress on (ME)CFS held in Brussels in November 1995, Hilgers and Frank developed a score for severity of ME/CFS to correlate with parameters of immune activation. This was effected by a 30-point criteria score, basic laboratory programmes and immunological profiles in 505 patients. In addition, tests of the complement system, immune activation markers, hormones and viral/bacterial intracellular serology were evaluated. **Seventeen significant symptoms not currently in the CDC case definition were added, these being respiratory infections, palpitations, dizziness, dyspepsia, dryness of mouth/eyes, allergies, nausea, paraesthesia, loss of hair, skin alterations, dyscoordination *(sic)*, chest pain, personality changes, eczema, general infections, twitches and urogenital infections. A significant correlation between the criteria score and immunological parameters could be evaluated in 472 of the 505 patients. The data confirm that a reduced or unstable immune control or delayed immune reaction to persisting viruses or bacterial intracellular pathogens, possibly triggered by common infections or other environmental factors, can lead to a chronic neuroimmune activation state and autoimmune disorders** (JCFS 1996:2: (4):35-47).

1996

The Third Biennial AACFS Clinical and Research Conference was held on 13th – 16th October 1996 in San Francisco (reported in 67 pages of the January 1997 edition of The CFIDS Chronicle, to which grateful acknowledgment is made).

Vicki L Carpman reported on the Endocrinology Sessions ("Stess-Associated Immune Modulation"), noting Dr Ronald Glaser's presentation that stress directly modulates the immune, endocrine and central nervous systems and that research has shown that stress can induce viral reaction in at least three ways. Dr Glaser made a recommendation to (ME)CFS researchers: "*The bottom line is that when (ME)CFS researchers have discussions about what immune markers to*

measure and why to measure them…my suggestion is to include the hormones because of their effect on immune function".

The Immunology Sessions included the following:

Theresa L Whiteside, Professor of Pathology at the University of Pittsburgh School of Medicine and Director of the Immunologic Monitoring Laboratory at Pitt's Cancer Institute, had applied her expertise in natural killer cell biology and immunology to the study of (ME)CFS. **She recommended stratifying (ME)CFS patients by immune profile, noting that the immune abnormality that has been most commonly found is low NK cell account and cytotoxic activity** (NK cells have a number of roles including defending against viruses, bacteria and tumours and interacting with the central nervous system). She said that in most diseases characterised by low NK cells such as cancer and AIDS, researchers understand the cause, but in (ME)CFS researchers do not know why NK cells are low. She concluded by saying she believes that (ME)CFS is actually a group of immune-mediated diseases and that the immune system may contribute to the pathogenesis.

Professor Nancy Klimas reported on her work investigating the role of cytokine abnormalities reported in (ME)CFS; **significant elevation of tumour necrosis factor receptor-type 1 (TNF R1) was found in the (ME)CFS samples and the data was also skewed for TNF α, IL-5 and IL-10. This pattern is similar to that found in autoimmune diseases and allergy.**

Dr Eng Tan (from the Autoimmune Disease Centre and Department of Cell Biology, the Scripps institute, La Jolla, California) **reported that of 60 (ME)CFS patients, 68% had evidence of anti-nuclear antibodies, an indication of autoimmune disease.**

Dr Konstantin N Konstantinov (Albuquerque, New Mexico) reported that his work ***"provides new laboratory evidence for an autoimmune component in (ME)CFS".***

Dr Richard Lanham (State University of New York) noted the incidence of autoimmune or other immunological disease in the families of patients with (ME)CFS, which was reported by 64% of (ME)CFS patients; Dr Lanham speculated that autoimmune conditions in the family history might be a predisposing factor for (ME)CFS.

Dr Edward Barker (University of California, San Francisco) had compared CD+ cell function in patients with (ME)CFS and controls; **CD69 expression on CD8+ cells was 58% in (ME)CFS patients whilst it was only 33% in controls. Specific lysis of anti-CD3 antibody-stimulated CD+ 8 cells was 62% in (ME)CFS and 32% in controls. The researchers concluded that "*(ME)CFS is associated with an increase in CD8+ cell activity following activation*" and that "*CD+8 cell dysfunctions can be common findings in individuals with (ME)CFS".***

Dr Neil Abbot et al (Scotland) carried out allergy and immune marker testing on patients with (ME)CFS and healthy controls, the (ME)CFS patients being stratified into three groups based on severity of symptoms. **When immune activation markers were measured, CD38 levels were elevated in the sickest patients compared with the other two patient groups.**

Dr Arnold Hilgers (Germany) compared immune panels in 285 (ME)CFS patients, 40 MS patients, 44 rheumatoid disease patients and 100 atopic (allergic) disease patients. 41-88% of (ME)FS patients had functional abnormalities. Food protein hypersensitivity (Type IV) was more common than viral infections in all the patients groups studied. The researchers explained that food protein hypersensitivity might cause chronic immune activation.

Dr Adrienne Bennett measured the four subclasses of IgG in a case-control study; **levels of IgG1, IgG3 or IgG4, and levels of IgG2 were higher in the (ME)CFS cases than controls.**

The Immunology Workshop. Professor Nancy Klimas and Dr Jay Levy moderated this 2-hour Workshop, the goal being to improve consistency among (ME)CFS research studies**. The Workshop's conclusions were:**

- **CD4, CD8, and NK cells should be included in the minimum immune panel. The activation markers DR, CD11, CD26, CD38 and CD69 and the cytokines IL-2, IL-4, IL-5,**

Il-6, IL-10 and IL-12 are of research interest

- **NK cell function should be measured as soon as possible following blood draw, within 4 hours**
- Researchers should consider the effect of the endocrine system on the immune system
- A chronic infection may be causing the immune activation seen in (ME)CFS patients.

1997

On 17th January 1997 Dr Darryl See (Head of the CFIDS Clinic at the University of California, Irvine) gave a lecture in Los Angeles entitled "New Concepts in Cause and Treatment of CFIDS", noting the low levels of IgG3 and IgG1 and the consequent loss of anti-viral activity, and the very, very low levels of IL-10 in people with (ME)CFIDS, pointing out that IL-10 is a down-regulator of the immune system and in normal people calms it down by decreasing the number of inflammatory cytokines. He also warned about taking prednisone: ***"You only take prednisone if you're in the T-cell activation group. If you have natural killer cell dysfunction, and you give a lot of prednisone, your NK cell activity will go down (further) and you'll start reactivating viruses. It's dangerous".***

1997

Dr Charles Shepherd from the UK ME Association published an article in the British Journal of Social Work (1997:27:755-760) in which he drew attention to the most relevant findings to date, including the immunological dysfunction in ME/CFS: "*Almost all reported studies have found laboratory abnormalities"*, citing Strober W (1994) "Immunological function in chronic fatigue syndrome"; in: Straus S (ed): Chronic Fatigue Syndrome; New York, Mark Dekker, pp 237-240.

1997

"The level of bioactive transforming growth factor β was measured in serum from patients with (ME)CFS and compared with normal controls, patients with major depression, patients with systemic lupus erythematosus and patients with multiple sclerosis. ***Patients with (ME)CFS had significantly higher levels of bioactive TGFβ than the healthy controls, patients with major depression, patients with systemic lupus erythematosus and patients with multiple sclerosis. Of greatest relevance to (ME)CFS are the effects of TGF β on cells of the immune and central nervous systems. There is accumulating evidence that TGFβ may play a role in autoimmune and inflammatory diseases****"* (AL Bennet, AL Komaroff et al. J Clin Virol 1997:17:2:160-166).

1997

"(ME)CFS is associated with dysregulation of both humoral and cellular immunity, including mitogen response, reactivation of viruses, abnormal cytokine production, diminished natural killer (NK) cell function, and changes in intermediary metabolites. The biochemical and immunologic data presented here identified a subgroup of individuals with (ME)CFS with an RNase L enzyme dysfunction that is more profound than previously observed (and) is consistent with the possibility that the absence of the 80-kDa and 40-kDa RNase L and presence of the LMW RNase L correlate with the severity of (ME)CFS clinical presentation*"* (Robert Suhadolnik, Daniel Peterson, Paul Cheney et al. Journal of Interferon and Cytokine Research 1997:17:377-385).

Professor Suhadolnik explained in lay terms the significance of this paper (reported by Patti Schmidt in CFIDS Chronicle, Summer 1997, page 17): "*He has found a particular place in the immune system, the 2-5 RNase L antiviral pathway, where something is wrong. 'The whole antiviral pathway heats up out of control' explained Suhadolnik.* ***'You're really sick physiologically. Your body just keeps going and going like the Energiser bunny, making ATP and breaking it down. No wonder you're tired'****. He's found a novel protein in CFIDS patients in that viral pathway. 'In most cases, the human body is able to resist infection thanks to a cascade of biochemical events triggered by the body's immune system. If these antiviral defence pathways are functioning correctly, the spread of the virus is prevented'.*

Suhadolnik believes that (ME)CFS patients' bodies are responding to a central nervous system virus that interferes with their viral pathways' ability to fight off infection ".

1997

On 16th August 1997 Professor Anthony Komaroff from Harvard made a presentation at North-Western Memorial Hospital, Chicago, where he summarised areas of the most exciting research. He said there were a number of biological and immunological measures that show promise and he was encouraged by the growing recognition of the disease as "*one of the brain and not one of the mind"*. He stated that there are objective physical abnormalities that occur in (ME)CFS, both neurological and immunological measures, mentioning specifically NK cells and autoimmune findings.

1997

A highly-respected paper by Vojdani and Lapp et al stressed the importance of cell apoptosis (and the pivotal role of protein kinase RNA in this) in ME/CFS: "***A prominent feature of (ME)CFS is a disordered immune system.*** *Recent evidence indicates that induction of apoptosis might be mediated in a dysregulated immune system by the up-regulation of growth inhibitory cytokines. The purpose of this study was to evaluate the apoptotic cell population, interferon-α and the IFN-induced protein kinase RNA (PKR) gene transcripts in the peripheral blood lymphocytes of (ME)CFS individuals, as compared to healthy controls.* ***One of the distinguishing manifestations of (ME)CFS is abnormal immune function, characterised by a decreased NK cell-mediated cytotoxic activity, reduced mitogenic response to lymphocytes, altered cytokine production, elevated titres of antibodies to a number of viruses, and abnormal production of interferon (IFN).*** *The induction of apoptosis through immune defence mechanisms is an important mechanism for elimination of cancer cells as well as virus-infected cells. In the present study, the up-regulation of IFN-α and the IFN-induced PRK in (ME)CFS individuals is accompanied by the induction of apoptosis. In addition, dysregulation of cell cycle progression is associated with the induction of apoptosis in (ME)CFS individuals.* ***Quantitative analysis of apoptotic cell population in (ME)CFS individuals has shown a statistically significant increase compared to healthy controls. The population of apoptotic cells in 76% of (ME)CFS individuals was well above the apoptotic cell population in the control cells.*** *Activation of PKR can result in induction of apoptosis. This activation of the PRK pathway could result from (a) dysregulated immune system or chronic viral infection"* (A Vojdani et al. Journal of Internal Medicine 1997:242:465-478).

1997

"***Previous studies from this laboratory have demonstrated a statistically significant dysregulation in several key components of the 2' 5'A synthetase / RNase L and PKR antiviral pathways in (ME)CFS.*** *The 2-5A synthetase / RNase L pathway is part of the antiviral defence mechanism in mammalian cells. An accumulating body of evidence suggests that (ME)CFS is associated with dysregulation of both humoral and cellular immunity, including mitogen response, reactivation of viruses, abnormal cytokine production, diminished natural killer (NK) cell function and changes in intermediary metabolites. Marked and striking differences have been observed in the molecular mass and RNase L enzyme activity of 2-5A binding proteins in extracts of PBMC from individuals with (ME)CFS compared with healthy controls.* ***The biochemical and immunological data presented in this paper have identified a potential subgroup of individuals with (ME)CFS with an RNase L enzyme dysfunction that is more profound than previously observed in (ME)CFS,*** *and which the authors believe is related to the severity of (ME)CFS symptoms"* (Daniel L. Peterson, Paul R. Cheney, Kenny de Meirleir et al; Journal of Interferon and Cytokine Research 1997:17:377-385).

1997

On 24th –26th October 1997 a CFIDS Association conference was held at St Charles, Illinois, attended by such luminaries as Drs Anthony Komaroff, Leonard Jason and Nancy Klimas.

Professor Komaroff said that researchers have become more interested in the immunological abnormalities, and among the more consistent findings are depressed activity of NK cells and increased number of certain T-cell. **Recent studies have found unusual antibodies attacking the nucleus of cells in (ME)CFIDS patients: "*These have not been seen with this frequency in other illnesses".***

Professor Klimas said that a temptation for doctors pondering how to approach treatment for (ME)CFIDS patients is to look at the activated immune system and try to calm it down, but *"the dilemma in (ME)CFS is that we don't know why that activity is there. We don't know if this activation is in response to something in the body that needs the immune system to protect it. You run the risk of suppressing the immune system so I don't think that's a fair target now for (ME)CFS treatment"* (The CFIDS Chronicle, January/February 1998).

1998

On 11th – 13th February 1998 a conference entitled "The Clinical and Scientific Basis of Chronic Fatigue Syndrome: From Myth towards Management" was held at Manly, Sydney, at which notable speakers included Dr David Bell, Dr Peter Rowe, Dr Martin Lerner, Dr Charles Lapp, Dr Byron Hyde, Dr Hugh Dunstan, Dr Neil McGregor, Dr Richard Burnet, Professor Gary Scroop and Professor Kenny De Meirleir. Speakers noted the detection of abnormalities in immunological measures including the CD4:CD8 ratio, an abnormality in NK cells and positive anti-nuclear antibodies. Colin Little presented a paper on the relationship of TGFβ and its relationship to fatigue and food intolerance, explaining that if small amounts of an ingested antigen (i.e. food) induce TGFβ and Th2 cells (which produce IL-4 and IL-10), then active suppression of protective Th1 cells occurs, with the result that patients experience intolerance/allergies to food, accompanied by autonomic symptoms.

1998

On 16th July 1998 Professor Stephen Straus from the USA gave a lecture at the Royal College of Physicians, London, in which he said: "*It is a disease that perhaps arises from immune dysfunction….**There are reasons to implicate immune problems in CFS…There are many published reports of a range of immune abnormalities – immunoglobulin deficiencies, increased levels of cytokines, abnormal T cell subsets and NK cells**".*

1998

"The increased expression of Class II antigens and the reduced expression of the co-stimulatory receptor CD28 lend further support to the concept of immunoactivation of T-lymphocytes in (ME)CFS and may be consistent with a viral aetiopathogenesis in the illness. ***We report, for the first time, increased expression of the apoptosis repressor protein bcl-2 (and) we demonstrated changes in different immunological parameters, each of which correlated with particular aspects of disease symptomatology (and) measures of disease severity****"* (IS Hassan, WRC Weir et al. Clin Immunol & Immunopathol 1998:87:1:60-67).

1998

The fourth Biennial AACFS International Research and Clinical Conference was held on 10th – 12th October 1998 at Cambridge, Massachusetts, with over 60 doctors and researchers attending.

Professors Klimas, Fletcher and Patarca et al described (ME)CFS as *"an illness which is associated with immune dysfunction, including abnormalities in the function of lymphocytes and expression of pro-inflammatory cytokines"* (Conference Proceedings, page 19).

Dr Eng Tan et al (from the Autoimmune Disease Centre and Department of Cell Biology, the Scripps institute, La Jolla, California) noted: "*In previous studies (J Clin Invest 1996:98:1888-1896; Arthritis Rheum 1997:40:295-305) it was found that patients with (ME)CFS had autoantibodies to a relatively insoluble cellular antigen localised at the nuclear envelope called lamin B1….(Results) suggested that there might be an epitope on lamin B1 that was specific for (ME)CFS…..**Conclusion:***

(ME)CFS patients have autoantibody responses which target epitope or epitopes in the N-terminal region of lamin B1" (Conference Proceedings page 26).

Drs Aristo Vojdani, Charles Lapp et al noted that ***"A prominent feature of (ME)CFS is a disordered immune system. Recent evidence indicates that induction of apoptosis might be mediated in a dysregulated immune system by the upregulation of growth inhibitory cytokines….Increased apoptotic cell population was observed in (ME)CFS individual as compared to healthy controls"*** (Conference Proceedings page 27).

S. Wagner, N Klimas et al: ***"The purpose of this study was to investigate the relationship between immunologic status and physical symptoms in (ME)CFS patients. The findings suggest that the degree of cellular immune activation is associated with the severity of (ME)CFS physical symptoms. Specifically, elevations in the T-helper/inducer cells, activated T-cells, activated cytotoxic/suppressor T-cells, and CD4/CD8 ratio are associated with greater disease severity"***. The immune system abnormalities were (i) a low percentage of cytotoxic T cells; (ii) a low number of cytotoxic T cells; (iii) a high percentage of T helper cells; (iv) a high number of T helper cells; (v) a high CD4/CD8 ratio; (vi) a high number of activated T cells; (vii) a high percentage of cytotoxic T cells; (viii) high numbers of activated T cells (Conference Proceedings page 28).

Professor Klimas said that the most important thing in this type of research is to carefully define the study population, and that the lack of definitional rigour may be the reason why study results have conflicted so widely.

She also talked about four possible causes of persistent immune activation: (i) a persistent virus, bacteria or toxin; (ii) autoimmune disease; (iii) a 'super-antigen' which turns on the entire immune system (e.g. silicone), and (iv) allergy.

She recommended that because the immune, endocrine and neurological systems are interdependent, scientists integrate their findings in (ME)CFS.

1999

On 23rd and 24th April 1999, a "Fatigue 2000" International Conference was held in London. There were 25 speakers, including several from the US as well as from Europe. Many aspects of ME/CFS were addressed, including the immunological dysfunction.

Professor Jonathan Brostoff (an immunologist and Director of the Centre for Allergy Research, University College, London) described the type of patient he saw at his clinics and discussed allergy in (ME)CFS. He was emphatic that environmental factors played a much more crucial role in (ME)CFS than has been acknowledged.

1999

"It is of great importance to develop biomarker(s) for differentiation between virally induced (ME)CFS (without sensitivity to chemicals) versus chemically-induced (ME)CFS. *Since interferon induced proteins 2-5A Synthetase and Protein Kinase RNA (PKR) have been implicated in the viral induction of (ME)CFS, the objective of this study was to utilise 2-5A and PKR activity for differentiation between (ME)CFS induced by either viruses or chemicals. A clear induction of 2-5A and PKR was observed when MDBK cells were exposed to HHV6, MTBE, and benzene.* ***We conclude that 2-5A and PKR are not only biomarkers for viral induction, but biomarkers to other stressors that include (chemicals)"*** (Vojdani A, Lapp CW. Immunopharmacol Immunotoxicol 1999:21(2):175-202).

1999

An article from researchers at the Institute of Immunology in Moscow discussed immunity impairment as a result of neurohormonal disorders and noted that at the base of (ME)CFS lie disturbances of the central nervous system, the endocrine system and the immune system: ***"It was found back in 1987/8 that there is an increase in the level of HLA DR and IL-2 receptors and an increase in the ratio CD4/CD8 in patients***

suffering from this syndrome" (Artsimovich NG et al. Russ J Immunol 1999:4(4):343-345).

It is notable that Russian researchers were aware of these cardinal biomarkers of (ME)CFS as long ago as 1999, but that eight years later, the NICE Guideline Development Group who produced the Clinical Guideline on "CFS" (who were clearly influenced by the Wessely School but who were acclaimed by NICE as "experts" in the disorder) were apparently unaware of these diagnostic biomarkers.

1999

The Second World Congress on (ME)CFS and Related Disorders took place on 9th-12th September 1999 in Brussels; as was the First World Congress in 1995, it was organised by Professor Kenny DeMeirleir. Medical experts from around the world presented their most recent findings in 48 oral and 26 poster presentations to an estimated 150 conference delegates.

Professor Nancy Klimas gave a comprehensive and authoritative overview entitled "Immunological Abnormalities in CFS". She started by listing various factors affecting the immune system in (ME)CFS: (i) genetic predisposition (51%); (ii) triggering events (infections), and (iii) mediators (endocrinological and psychological factors), observing that the health outcome in any individual depends on how all these interact.

She said the role of the immune system in illness is twofold:

(1) it plays a direct role in contributing to the symptom complex: immune competence decides effective or defective prevention of reactivation of infections. When turned on, the lymphocyte antigen-driven response may generate a Type I response (CD4+, Th1, IL 2 / IL 12, INF - gamma, with activation of CD8+ cells that kill viruses). Lymphocytes play a vital role: they function through a messenger system -- cells have memories; they are antigen-driven and recognise infections, transplants, toxins, foods etc.

(2) it plays an indirect role, because it interacts with the brain (it has receptors for neurotransmitters) and with the endocrine system. Cortisol reduces inflammation through down-regulation of immune activation -- **low cortisol in CFS could play a role in chronic immune activation**. Stress has a profound impact on the immune system. Interaction with the hypothalamic/pituitary axis affects neurotransmitters and impacts on sleep. **The Type II response (Th2, IL6, IL10, activation of B cells, and antibody production, which prevents/clears infection) comes to dominate as the illness extends.**

The importance of the 2-5 RNase -L (a product of INF- gamma activation) leads to an up-regulation of RNA synthesis and pro-inflammatory cytokines, TNF -alpha and IL 1, which also disturb circadian rhythms.

Specific oligoclonal and not polyclonal antibodies are involved. With regard to oligoclonal versus polyclonal activation, Professor Klimas observed that there is a lack of abnormal serology to most latent viruses, suggesting that immune activation was antigen-specific.

The effects of stress and negative life events were similar in CFS patients and in controls, but **the long-term outcome depends on the shift from Th1 to Th2.**

There is evidence of chronic immune activation: enzyme systems are up-regulated (e.g. interferon, 2-5A RNase L activation, mRNA (cytokines).

There is evidence of cytokine abnormalities – cytokines change over time and with illness severity: TNF-alpha receptor expression increases with flares of the illness, and there is increased evidence of Type II expression as the illness persists for years.

Long-term, stress results in immune dysfunction illness (e.g. reduced numbers of CD8 (suppressor) cells, blunted growth hormone (GH) response and thyroid releasing factor (TRF),

and increased corticotrophin releasing factor (CRF).

Professor Klimas said (ME)CFS was an excellent model of neuroendocrine-immune interaction and re-stated the PNI (psychoneuroimmunological) paradigm as a basis for understanding the complex relationships which underlie the extensive changes occurring in (ME)CFS patients.

She concluded by confirming that immune abnormalities play an integral role in the pathogenesis of (ME)CFS and that they contribute to the symptom complex, and that they interact with the autonomic and endocrine systems; the pattern and type of immune activation are equal to "cause and effect".

Following this conference, on 19th October 1999 The Medical Post (volume 35, number 35) published an article pointing out that, according to a US study by Professor Paul Levine from George Washington University that was presented at the Second World Congress on CFS and Related Disorders, patients with (ME)CFS who show signs of recent immunosuppression should be monitored for certain types of cancer: ***"This study suggests that immune dysfunction is an important aspect of at least one CFS subgroup….according to Dr Levine, the types of cancer reported included B-cell lymphoma, brain tumours, adenoid cystic carcinoma of the breast, transitional carcinomas of the bladder, uterine cancer, basal cell carcinoma… and non-Hodgkin's lymphoma. Two (patients) reported multiple primaries. 'These weren't the type of cancers you'd see in a typical population' (said Dr Levine)….The mechanism for this effect might involve natural killer cell activity, Dr Levine said. People with (ME)CFS have decreased (NK) activity, which is associated with cancer"***.

2000

"The purpose of the present study was to investigate the relationship between immunologic status and physical symptoms in (ME)CFS. ***(Results) revealed significant associations between a number of immunologic measures and severity of illness. Specifically, elevations of T-helper/inducer cells, activated T cells, activated cytotoxic/suppressor T cells, and CD4/CD8 ratio were associated with greater severity of several symptoms. Furthermore, reductions in T-suppressor/cytotoxic cells also appeared related to greater severity of some (ME)CFS-related physical symptoms and illness burden"*** (SE Cruess, Nancy Klimas et al. JCFS 2000:7(1):39-52).

2000

"Most long-term sufferers (ill an average of 16 years)…showed a higher percentage of infection with viral and immune-related illnesses including allergies" (Friedberg F et al. J Psychosomatic Res 2000:48:59-68).

2000

"Over the past 15 years, scientists have identified numerous biological abnormalities that provide evidence for the reality and seriousness of (ME)CFS….In particular, they have provided evidence that the illness involves both the brain and the immune system*….The leading model of (ME)CFS pathogenesis is rooted in scientifically identified abnormalities in the brain (central nervous system) and the immune system….****Low levels of circulating cortisol, identified in several (ME)CFS research studies, can increase immune activation, which is also a key feature of (ME)CFS****….Several immune system patterns are seen more often in patients with (ME)CFS. The identified abnormalities mimic the immune pattern of a body fighting a virus….(and include) low NK cell function (and) elevated immune complexes.* ***The most intriguing recent immunological finding in (ME)CFS is the discovery of a novel low molecular weight protein in an antiviral pathway called the RNase-L pathway. This novel protein is found much more often in (ME)CFS patients than in healthy controls"*** (Anthony L Komaroff. The CFS Research Review, Spring 2000:1: 1-3).

2000

In 2000 Professor Anthony Komaroff from Harvard wrote about Professor Kenny De Meirleir's work on RNase L in an Editorial in the American Journal of Medicine: ***"What is this research telling us? It is another piece of evidence that the immune system is affected in chronic fatigue syndrome and it reproduces and extends the work of***

another investigator (Professor Suhadolnik from the US), lending credibility to the result" (Am J Med 2000:108:169-171).

(Belgian research has focused on the abnormal enzyme pathways and 88% of (ME)CFS patients tested positive for RNase L. The 37kDa is produced by calpain cleavage, and the whole process affects the calcium and potassium ion channel mechanisms. **RNase L is a likely marker for (ME)CFS and correlates with severity. It is negative in AIDS --** with acknowledgement to Dr Rosamund Vallings).

2000

"Blood and lymph nodes samples were obtained from patients with (ME)CFS. While a greater proportion of T lymphocytes from both lymph nodes and peripheral blood of (ME)CFS patients are immunologically naïve, the proportions of lymphocytes with a memory phenotype predominate in lymph nodes and peripheral blood of (ME)CFS patients. ***(ME)CFS has been proposed to be a disease of autoimmune aetiology and in this respect it is interesting to note that decreased proportions of CD45RA+T (naïve) cells are also seen in the peripheral blood of patients with autoimmune diseases"*** (Mary Ann Fletcher, Nancy Klimas et al. JCFS 2000:7(3):65-75).

2000

A major and detailed Review of the immunology of (ME)CFS was published by internationally-renowned immunologists Professors Robert Patarca and Nancy Klimas, together with the distinguished long-time ME/CFS research immunologist Professor Mary Ann Fletcher. It contains 212 references. **It is clear that people with (ME)CFS have two basic problems with immune function: (1) immune activation and (2) poor cellular function**. These findings have a waxing and waning temporal pattern consistent with episodic immune dysfunction. The interplay of these factors can account for the perpetuation of (ME)CFS with remission/exacerbation cycles. The Review considers the evidence of immune cell phenotypic distributions; immune cell function; cytokines and other soluble immune mediators; immunoglobulins; autoantibodies; circulating immune complexes; Type I to Type II cytokine shift and the relationship between stressors, cytokines and symptoms. **The data summarised indicate that (ME)CFS is associated with immune abnormalities that can account for the physiopathological symptomatology, and recommends that future research should further elucidate the cellular basis for immune dysfunction in (ME)CFS and its implications** (JCFS 2000:6(3/4):69-107).

2000

The US National Institutes of Health held a State of the Science Conference on (ME)CFS on 23rd-24th October 2000 in Arlington, Virginia, and was attended by more than 200 people. The conference was divided into six topic areas: neuroendocrinology, neurocognition, pain, immunology, fatigue and orthostatic intolerance. Panelists included well-known (ME)CFIDS physicians such as Drs Nancy Klimas, David Bell, Dedra Buchwald and Peter Rowe. The Immunology section was described in the UK ME Association's magazine "Perspectives" (Spring 2001) as the most interesting. It was noted that (i) previous studies suggested that the immune system and immune modulators (the chemical cascade that stimulates the immune system to act) are involved in the process of the illness; (ii) HLA markers are more common in (ME)CFS patients and these markers could be associated with autoimmune disease; (iii) **the chemicals of the immune system may be directly or indirectly linked to symptom expression;** (iv) NK function is low; (v) some classes of IgG are low; (vi) a CD3 receptor may have reduced expression in (ME)CFS patients; (vii) **there is a shift during the illness from cell-mediated immunity to humoral immunity (antibody-based), and this pattern is associated with autoimmune disease and chronic infection.** The conference concluded with the expert panel summarising (ME)CFIDS research needs, **most notably that researchers must subgroup patients by unique features such as immunology.**

2000

"There is now so much literature from so many varying aspects of biology in ME/CFS that it is simply not possible to summarise it all in a paragraph or two. ***By calling the illness CFS we***

start with a conundrum – the name. This is a small point to many academics and clinicians but to sufferers and researchers alike it is at the hub of the enigma in terms of treatment and management and, also, for the researcher in the classification and definition of cohorts – the hallmark of good science….ME is a neurological illness (WHO ICD 10 G93.3) with evidence of immunological and toxicological signs, clear disturbance to the neuro-endocrine stress axis, impairment of the autonomic nervous system, irregularities in perfusion to the brain and indeed to the peripheral vascular system….A review of the literature on the immunology of (ME)CFS (Patarca-Montero R et al: JCFS 2000:6:69-107) reveals that people who have more strictly defined CFS equating with ME have two basic problems with immune function that have been documented by most research groups: 1. immune activation, as demonstrated by elevation of activated T lymphocytes, including cytotoxic T cells, as well as elevations of circulating cytokines, and 2. poor cellular function, with low NK cell cytotoxicity, poor lymphocyte response to mitogens in culture, and frequent immunoglobulin deficiencies, most often IgG1 and IgG3*…..Although the causes of ME/CFS remain to be elucidated, **many studies provide evidence for abnormalities in immunological markers among patients….Although a subset of patients with immune activation can be identified, serum markers of inflammation and immune activation are said by advocates of the psychiatric aetiology to be of limited diagnostic usefulness in the evaluation of patients with ME/CFS (even though) ME/CFS patients can be categorised by immunological findings….The same psychiatrists carelessly or expediently ignore the increasing evidence for the physical case for ME/CFS**"* (Research Report in ME/CFS for the Fife Health Board, Scotland. Dr Vance A Spence. November 2000).

2001

The Fifth Biennial International AACFS Research and Clinical Conference was held in Seattle from 26th – 29th January 2001. From the Immunology sessions, the following are highlighted:

Professor Kenny De Meirleir (Brussels) presented evidence that **a large number of (ME)CFS patients have an abnormal immune profile; this altered immune system can result in the production of immunologic mediators such as interferons, interleukins and other cytokines. Recently, an up-regulation of the 2-5A Synthetase/RNase L pathway has been shown in (ME)CFS patients, indicating an activated immune state.** According to their immununologic profile, patients were divided into three groups and significant differences were found for IFN gamma between groups 2 and 3 and between the controls and group 3. The presence of an increased amount of LMW (low molecular weight) RNase L correlated with higher levels of IFN gamma, which has anti-viral properties (Conference Proceedings # 017).

Drs K Sugiura, A Komaroff, Eng Tan et al **reviewed autoimmunity in (ME)CFS and reported on a multi-centre study. Low titres of antinuclear antibodies have been found in (ME)CFS. The study looked at the presence of autoantibodies to a cellular protein expressed primarily in neuronal cells, MAP2 (a microtubule-associated protein). Initial studies with immunohistochemistry showed a high percentage of (ME)CFS sera reactive to centrosomes. Evidence shows that other proteins besides MAP2 might also be target antigens in (ME)CFS autoimmunity. Of interest was the high frequency of reactors with lupus erythematosus and rheumatoid arthritis compared with (ME)CFS patients** (Conference Proceedings #037).

Drs Kevin Maher, Nancy Klimas and Mary Ann Fletcher presented on "Flow Cytometric Measurements of Perforin and Natural Killer Cell Activity": **the intracellular content of the Natural Killer (NK) cell is perforin, a cell lytic protein common in many cells of the immune system which correlates with the cytolytic potential of the cell. In (ME)CFS, this chemical is reduced in NK cells**. This finding substantiates claims of an NK associated defect in (ME)CFS and suggest a molecular basis for the reduced cytotoxicity (immune system killer cell function). This defect may not be NK specific but may encompass the cytotoxic T cell subset as well. **Mice which were genetically engineered to have low or absent levels of perforin showed the same immune abnormalities as (ME)CFS. Other abnormalities**

found include activated lymphocytes in various subsets, elevated levels of immunoglobulins (IgG in particular) and increased levels of immune molecules called pro-inflammatory cytokines (Conference Proceedings #047).

Drs Patrick Englebienne, Kenny De Meirleir et al provided evidence of apoptosis (programmed cell death) in (ME)CFS that has been suggested to contribute to the symptomatology. **RNase L has been directly linked to the induction of apoptosis. This study showed that the activation of RNase L in the PBMC (peripheral blood mononuclear cells) of (ME)CFS patients up-regulates apoptotic activity in these cells. This suggests that the perturbed apoptotic process may play a role in the altered immunologic function in (ME)CFS** (Conference Proceedings #068).

The final session on 28th January 2001 was a name-change open forum (Professors Nancy Klimas, Leonard Jason and Charles Lapp) because a new and more appropriate name than "chronic fatigue syndrome" was deemed necessary: the Committee came to the view that there was enough scientific evidence to base a new name on the fact that this illness has neurological, immunological and endocrine components, hence the suggestion of NIEDS (neuro-immune-endocrine dysfunction syndrome, which describes the underlying pathology) to replace CFS.

This conference was reported in The CFIDS Chronicle, Spring 2001:14:2:1-6 and also in The CFS Research Review Spring 2001:2:2:4-8.

2001

In his "Directions in Immunotherapy", Professor Roberto Patarca-Montero from the University of Miami School of Medicine said: ***"In a subset of (ME)CFS patients, the immune system is always activated…One hypothesis is that it is caused by a lingering infection or an infection that leaves autoimmune sequelae. Although the immune systems of some (ME)CFS patients are chronically activated, parts function poorly****, particularly the T cells and natural killer cells….(ME)CFS patients' T cells have a decreased capacity to divide and generate new T cells, and their NK cells have significantly decreased cytotoxic activity.* ***In (ME)CFS, the immune system is based on the type of response T cells mount to infection.*** *Two types of T-helper cells boost the immune attack – T-helper type 1 (Th1) cells and T-helper type 2 (Th2) cells. The Th-1 cells stimulate macrophages and NK cells, which directly attack microbes that replicate in the body's tissues. This type of response is called cellular immunity. Th2 cells attack foreign matter too large to be killed by macrophages or NK cells by preferentially stimulating B cells to produce antibodies. This type of response is called humoral immunity.* ***In (ME)CFS, as in many autoimmune diseases, the body tends to mount a humoral response. Activated T-helper cells from (ME)CFS patients produce fewer Th-1 cytokines (substances that convey messages to other cells and mediate their function) and produce more interleukin-5, a Th-2-type cytokine. Several therapeutic interventions are being studied to help reverse this unfavourable cytokine expression in (ME)CFS patients"*** (The CFS Research Review Winter (January) 2001:2:1:1).

2001

"*Of significant interest was the fact that, of all the cytokines evaluated, the only one to be in the final model was IL-4 (which) suggests a shift to a Type II cytokine pattern. Such a shift has been hypothesised, but until now convincing evidence was lacking"* (Hanson et al; Clin Diagn Lab Immunol 2001:8(3)658-662).

2001

"There is considerable evidence already that the immune system is in a state of chronic activation in many patients with (ME)CFS" (Anthony Komaroff, Assistant Professor of Medicine, Harvard Medical School: American Medical Association Statement, Co-Cure, 17 July 2001).

2001

In late autumn 2001 a Symposium on the immune system in (ME)CFS convened, with a panel of experts co-chaired by Dr Timothy Gerrity (Georgetown University Medical Centre) and Dr Dimitris Papanicolaou, (Emory University, Atlanta) and participants including Professors Nancy Klimas, Anthony Komaroff and Leonard Jason. It

was sponsored by The CFIDS Association, the US Centres for Disease Control, and the National Institutes of Health Office of Research on Women's Health and was the third in a series of scientific symposia on (ME)CFS. This series of (ME)CFS assessment symposia series was designed to examine the role of the neurological, endocrine, circulatory and immune systems in (ME)CFS. The Immune System symposium developed a strategy on key issues surrounding the immune system in (ME)CFS, with agreement on the following: (i) **The immune system is involved in (ME)CFS: substantial published evidence shows that many (ME)CFS patients have immunological abnormalities;** (ii) **infections may also play a role: the panel concluded that direct and indirect evidence points to the involvement of active viral or bacterial infections in some case of (ME)CFS;** (iii) **(ME)CFS is a multi-system disorder: in addition to the immune system, the endocrine and autonomic nervous systems may be implicated** and (iv) **more research is needed to define the immunological aspects of (ME)CFS. The symposium particularly noted *"the inappropriate practice of combining patients with…various comorbid conditions in studies and then attempting to draw conclusions across the subgroups"*** (The CFIDS Chronicle, Winter (January) 2002; The CFS Research Review, Winter (January) 2002:3:1).

2001

In December 2001 The Alison Hunter Memorial Foundation (AHMF) hosted the third international ME/CFS Research and Clinical Scientific Meeting in Sydney, Australia; the AHMF is an enduring memorial to Alison Hunter and to all those whose lives have been devastated by ME/CFS. Alison died aged 19 in 1996 from severe ME, suffering seizures, paralysis, gastrointestinal paresis, severe recurrent mouth ulcers and overwhelming infection, having courageously fought ME/CFS for ten years.

Professor Anthony Komaroff (Harvard) spoke on "The Biology of ME/CFS", noting that immune abnormalities are seen more often in patients, including low levels of circulating immune complexes, elevated total complement (CH50), elevated IgG, atypical lymphocytosis and low levels of antinuclear antibodies (ANA). Immunological studies have revealed a variety of immunological abnormalities, especially impaired function of natural killer cells and increased numbers of activated CD+T cells. Whilst neither finding is specific enough to constitute a diagnostic marker, they are nevertheless consistent with a chronically activated immune system in ME/CFS. **Two groups have reported what appears to be a more specific immune system abnormality in ME/CFS: an increased activity of the 2-5A enzymatic pathway in lymphocytes**. Patients with ME/CFS were very different from those with depression, fibromyalgia and healthy controls. The evidence indicates an organic basis, with abnormal regulation of the immune system.

Dr Patrick Englebienne and Professor Kenny De Meirleir (Brussels) spoke on "CFS and MS as Subsets of a Group of Cellular Immune Disorders". Apoptosis (programmed cell death) is a critical component of adaptive cellular immunity. When challenged by infection, type I interferons elicit apoptotic responses by inducing the expression of 2-5A synthetase (2-5OAS), RNaseL and the p68 dependent kinase (PKR). **Results from the authors' laboratories point to an improper activation of 2-5OAS in monocytes of both patients with ME/CFS and with chronic (but not in relapsing/remitting) MS, which results in an inappropriate activation of RNaseL. This process ultimately leads to a blockade of the RNaseL-mediated apoptotic programme and it supports the involvement of environmental factors.** Such cellular stress is capable of generating small RNA fragments and/or of inducing the transcription of endogenous retrovirus sequences. **The 'abnormal' RNA sequences are responsible for the inappropriate activation of 2-5OAS and have been implicated in the aetiology of both ME/CFS and MS.** Depending on their origin and structure, these RNA fragments are capable of either activating or down-regulating PKR. This results in a differential effect not only on the PKR/RNaseL-mediated apoptotic programmes but also on the activation by PKR of the inducible NO (nitric oxide) synthetase. **A release of nitric oxide at either high rates (as in ME/CFS) or low rates (as in chronic MS) by lymphocytes has corollary consequences, triggering the skeletal and cardiac muscle ryanodine receptors (calcium channels), NK cell function, COX2 activation and glutamate release by activated T-cells in the brain. Glutamate**

upregulation leads to oligodendrocyte excitotoxicity in MS, whilst glutamate downregulation in ME/CFS impairs hypothalamic CRH secretion. These results suggest that ME/CFS and MS are extremes of an array of dysfunctions in the 2-5A/RNaseL/PKR pathways into which other autoimmune diseases such as lupus erythematosus might fit.

Dr Pascale de Becker (Belgium) presented a poster showing that a number of different stressors and consequent immunological and neuro-endocrinological changes can contribute to the onset of ME/CFS.

C.H. Little (Mt Waveney, Victoria, Australia) said that their laboratory has identified a separate class of immune products (T cell antigen binding molecules) which may be the basis for adverse reactions experienced by some patients to foods. **Research indicates that an appropriate immune response to ingested food proteins is an absence of both Th1 and Th2 immune responses. This outcome (i.e. no response) may depend on antigen-specific regulatory cells whose function is to maintain tolerance to food proteins. The presence or absence of an immune response depends critically on signals delivered by special antigen-presenting cells (dendritic cells). This process can be potentially disrupted by environmental influences.**
(With grateful acknowledgement to Dr Rosamund Vallings from New Zealand).

2002

In an article entitled "CFS Research: The Need for Better Standards", Professor Nancy Klimas was unequivocal: "***Research effort is hampered by poorly conceived, constantly changing – even non-existent – standards….Authors of the 1988 case definition set out to identify a group of patients sharing similar symptoms and clinical signs, but problems using the definition quickly became apparent. A revision in 1994*** (i.e. the Fukuda CDC definition, with which the Wessely School was involved) ***…attempted to address some of the difficulties, but the resulting guidelines are rife with ambiguity and vagueness. Symptoms are counted as either present or absent, without regard to severity or frequency….The use by some groups of outdated case criteria developed in England*** (the Wessely School's Oxford criteria) ***and Australia obscures comparability….A stronger research effort will enhance credibility for the illness….Overcoming the methodological challenges of studying (ME)CFS is essential to making progress in understanding this complex illness and to uncovering more direct means of diagnosis and effective treatments"*** (The CFS Research Review 2002:3:2:5-7).

It is worth recalling that, eight years earlier, the Report of The UK The National Task Force (see above) **stated exactly what Professor Klimas needed to repeat in 2002: the Task Force Report was unequivocal in concluding that progress in understanding (ME)CFS is hampered by the use of heterogeneous study groups and definitions of CFS; by the lack of adequate comparison groups; by the lack of standardised laboratory tests, and by the invalid comparison of contradictory research findings stemming from these factors.**

Research has shown that using the Holmes et al CDC 1988 criteria, 80% may have (ME)CFS; using the Fukuda et al CDC 1994 criteria, 40% may have (ME)CFS, and using the 1991 Oxford (Wessely School) criteria, 10% may have (ME)CFS; the Australian criteria give roughly the same results as the Oxford criteria (Co-Cure RES.MED, 3rd December 2002: New Canadian clinical definition – ME/CFS).

It is also worth recalling Professor Wessely's published view that *"It is usual to try to discover the causes of an illness before thinking about treatments. Some illnesses are treated without knowledge of the cause…examples include… chronic fatigue syndrome"* (New Research Ideas in Chronic Fatigue. Ed: Richard Frackowiak and Simon Wessely for The Linbury Trust; pub: The Royal Society of Medicine, 2000). **This is in direct contradiction to Professor Klimas' (and other biomedical researchers') call for progress in understanding such a complex illness in order to find effective treatments.**

2002

"The present review examines the cytokine response to acute exercise stress. The magnitude

of this response bears a relationship to the intensity of effort but many environmental factors also modulate cytokine release. ***The main source of exercised-induced IL-6 production appears to be the exercising muscle. Cytokine concentrations are increased in (ME)CFS. Exercise-induced modulations in cytokine secretion may contribute to allergies (and) bronchospasm****"* (Shepherd RJ. Crit Rev Immunol 2002:22(3):165-182).

2002

In 2002 an important book was published by CRC Press: "**Chronic Fatigue Syndrome – A Biological Approach"** edited by Patrick Englebienne and Kenny De Meirleir. It provides a technical treatise on the scientifically documented basis of (ME)CFS and includes advances not only in the immunology, but also in the virology, bacteriology, protein chemistry and biochemistry, physiology and metabolism, clinical biology, pharmacology and epidemiology of (ME)CFS.

2003

On 31st January – 2nd February 2003, the Sixth Biennial AACFS International Research and Clinical Conference was held at Chantilly, Virginia. The number of oral and poster presentations (44 and 47 respectively) was down from the 2001 conference (72 and 41 respectively) and from the 1999 conference (57 and 46 respectively), but the conference was attended by over 190 physicians and health professionals from more than 14 countries, including Professors Anthony Komaroff, Leonard Jason, Robert Suhadolnik, Benjamin Natelson, Charles Lapp and Dr Daniel Peterson.

Dr Kevin Maher (University of Miami Medical School) described his work to determine the molecular mechanisms underlying the decreased NK cell cytotoxicity found in (ME)CFS patients, including activated T cells, elevated cytokines and immunoglobulins and reduced NK cell activity. His studies demonstrated significantly elevated expression of the activation molecule CD26 on T-helper cells and significantly reduced NK cell cytotoxicity relative to controls. **His studies concluded that perforin and granzymes A and B (used by T cells for killing infected cells) were significantly reduced in the T cells of (ME)CFS patients, and that activation of T cells is correlated with increased IL-4 and with decreased IL-6 that are typically seen in (ME)CFS patients**. In addition, the data suggest that the cytotoxic defect may not be NK specific but may encompass the cytotoxic T cell subset as well (with grateful acknowledgement to Drs Charles Lapp, Rosamund Vallings and Neil Abbot).

Dr Patrick Gaffney (Department of Medicine, University of Minnesota) demonstrated that white blood cells from patients with (ME)CFS exhibit distinct gene expression profiles, with differential regulation of 54 genes between patients with (ME)CFS and normal healthy controls.

2003

In Spring 2003 the Canadian Clinical Case Definition was published ("Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnosis and Treatment Protocols". JCFS 2003:11(1):7-115). It was developed by an international Expert Consensus Panel of physicians who are world leaders in ME/CFS and who between them had diagnosed and/or treated more than 20,000 ME/CFS patients. It presents a systematic clinical working case definition that encourages a diagnosis based on characteristic patterns of symptom clusters that reflect specific areas of pathogenesis; **in particular, it differs from previous definitions in that it includes the hallmark symptom of (ME)CFS (post-exertional fatigability and malaise)** and requires the presence of pain, sleep disturbance and cognitive dysfunction, and at least one of the given symptoms from two of the categories of neurological/autonomic, neuro-endocrine and immune manifestations. The expert panel member specialising in immunology was Professor Nancy Klimas. **It was widely acclaimed internationally by clinicians, scientists and patients alike, but in the UK the Wessely School actively opposed its use within the NHS and Departments of State, with the result that NICE recommended against its use in its 2007 Clinical Guidelines on "CFS".**

(Markedly different from the situation in the UK, a commissioned Report to the New Zealand Ministry of Health, November 2003, found that: "*Of all the*

guidelines reviewed, this was the one which the reviewers were most enthusiastic to recommend for adaptation in New Zealand…. Rigorously produced and published in a peer-reviewed journal, the (Canadian) guidelines have a good, comprehensive and up-to-date evidence-based, well-referenced. The reviewers also found the Canadian guideline to be written with compassion and understanding for people with (ME)CFS…and that it adopted a more balanced…model of (ME)CFS").

2003

On 12th-13th June 2003 a scientific workshop was held on "Neuro-Immune Mechanisms and CFS" at the Bethesda Marriott Hotel; it was hosted by the NIH and was designed to enhance understanding of (ME)CFS by examining the interface between the brain, the immune system, and the symptoms of (ME)CFS.

Dr Esther Sternberg (Director of the Integrative Neural Immune Programme and Chief of the Section on Neuroendocrine Immunology & Behaviour at the NIH) spoke on "Health Consequences of a Dysregulated Stress Response". A summary of her presentation by Rich Van Konynenburg was published on Co-Cure RES on 2nd July 2003.

Firdhaus Dhabhar (Associate Professor at Ohio State University) spoke about the effects of stress in people with (ME)CFS and noted that the problems with stress and the immune system occur when the stress situation is long-term.

Professor Nancy Klimas spoke on the immune dysfunction observed in (ME)CFS. She said **there is a lot of data indicating that there is chronic immune activation in (ME)CFS, that there is a fair amount of data indicating that there is a shift from Th-1 to Th-2 type of immune response (which means that in (ME)CFS, the Th-1 response that kills infected cells is missing), that there is considerable data showing that there are changes in cytokine expression, and there is a lot of data showing lowered NK cell cytotoxicity. In addition, there is evidence for elevated numbers of immune complexes, elevated levels of antinuclear antibodies (ANA), higher prevalence of allergies, and an activated RNase L pathway. Professor Klimas noted that there is a correlation between immune parameters and symptoms. In particular, when low NK cell activity and elevated T-cell activation are combined together, this correlates well with increased symptoms severity, and those with lower NK cell function had more severe fatigue and worse cognitive function. She also spoke about her group's finding that NK cells in people with (ME)CFS are low in perforin (the substance normally used by NK cells to punch holes in infected cells in order to inject granzymes into them to kill them). She once again mentioned the problems resulting from the study of heterogeneous populations and from non-standardised methodology** (Reported by Rich Van Konynenburg on Co-Cure RES, 3rd July 2003).

2003

A study was carried out by Belgian researchers to determine whether bronchial hyper-responsiveness (BHR) in patients with (ME)CFS is caused by immune system abnormalities. Measurements included pulmonary function testing, histamine bronchoprovocation test, immunophenotyping and ribonuclease (RNase) latent determination. There were 137 (ME)CFS participants. ***"Seventy three of the 137 patients presented with bronchial hyper-responsiveness. The group of patients in whom BHR was present differed most significantly from the control group, with eight differences in the immunophenotype profile in the cell count analysis, and seven differences in the percentage distribution profile. We observed a significant increase in cytotoxic T-cell count and in the percentage of BHR+ patients. Immunophenotyping of our sample confirmed earlier reports on chronic immune activation in patients with (ME)CFS compared to healthy controls, (with) BHR+ patients having more evidence of immune activation***" (Nijs J, De Meirleir K, McGregor N et al. Chest 2003:123(4):998-1007).

2003

Japanese researchers focused on immunological abnormalities against neurotransmitter receptors

in (ME)CFS using a sensitive radioligand assay. They examined serum autoantibodies to recombinant human muscarinic cholinergic receptor 1 (CHRM1) and other receptors in patients with (ME)CFS and the results were compared with those in patients with autoimmune disease and with healthy controls. **The mean anti-CHRM1 antibody index was significantly higher in patients with (ME)CFS and with autoimmune disease than in controls. Anti-nuclear antibodies were found in 56.7% of patients with (ME)CFS. The patients with positive autoantibodies to CHRM1 had a significantly higher score of 'feeling muscle weakness' than negative patients among (ME)CFS patients. The authors conclude: "*Autoantibodies to CHRM1 were detected in a large number of (ME)CFS patients and were related to (ME)CFS symptoms. Our findings suggest that subgroups of (ME)CFS are associated with autoimmune abnormalities of CHRM1*"** (Tanaka S, Kuratsune H et al. Int J Mol Med 2003:12(2):225-230).

2003

Looking at complement activation in (ME)CFS in the light of the need to identify biological markers in (ME)CFS, US researchers used an exercise challenge to induce symptoms of (ME)CFS and to identify a marker that correlated with those symptoms. "***Exercise challenge induced significant increases of the complement split product C4a at six hours after exercise only in the (ME)CFS group***" (Sorensen B et al. J All Clin Immunol 2003:112(2):397-403).

2003

"(ME)CFS is an increasing medical phenomenon leading to high levels of chronic morbidity. *The aim of this study was to screen for changes in gene expression in the lymphocytes of (ME)CFS patients. In a small but well-characterised population of (ME)CFS patients, differential display has been used to clone and sequence genetic markers that are over-expressed in the mononuclear cells of (ME)CFS patients.* ***Many researchers have recognised that current methods of diagnosis lead to the selection of a heterogeneous sample, and these data support that view.*** *It is encouraging that the wide 'spread' of data seen in (ME)CFS patients is not seen in the control samples.* ***The data presented here add weight to the idea that (ME)CFS is a disease characterised by over-expression of genes, some of which are known to be associated with immune system activation.*** *Identifying the triggering events for the induction of these genes will increase our understanding of this disease.* ***Some interesting possibilities include viral infection, neuroendocrine disturbances, and allergen exposure. A link with allergy may be particularly pertinent since approximately 80% of (ME)CFS patients are atopic. Some of the genes identified in this study may therefore be linked with the increase in allergic effects seen in (ME)CFS***" (R Powell, S Holgate et al. Clin Exp Allergy 2003:33:1450-1456).

2003

In an Invited Review, Patrick Englebienne from the Department of Nuclear Medicine, Vrije University, Brussels, explained in simple terms the significance of RNase L: *"RNase L (2-5-oligoadenylate-dependent ribonuclease L) is central to the innate cellular defence mechanism induced by Type I interferons during intracellular infection. In the absence of infection, the protein remains dormant. Recent evidence indicates, however, that the protein is activated in the absence of infection and may play a role in cell differentiation (and) immune activation.* ***A de-regulation of this pathway has been documented in immune cells of (ME)CFS patients. This protein escapes the normal regulation (resulting in) a cascade of unwanted cellular events.*** *Recent data indicate that the RNase L system role is not limited to the cell defence mechanism against intracellular infection but extends to the complete innate and adaptive immune systems, including NK and T-cell proliferation and activation, as well as to cell differentiation and proliferation.* ***The presence of unregulated active RNase L fragments in immune cells may lead to deleterious effects which are inherent to the cellular targets of the protein (because) an unregulated destruction of rRNA and of mitochondrial RNA leads to cell apoptosis. Should the RNase L de-regulation exist in muscle cells, it would necessarily restrain normal muscular development and hence activity (and) muscular weakness is a common feature of (ME)CFS***" (JCFS 2003:11(2):97-109).

2004

A study of immunological aspects of ME/CFS by Wessely School psychiatrist Professor Peter White et al deserves particular attention: this is because he was Chief Principal Investigator (PI) of the PACE Trial and despite his prior knowledge of the immune abnormalities associated with exercise in ME/CFS patients, the PACE Trial did not use that evidence but instead focused on attempting to prove that correction of patients' "aberrant illness beliefs" and graded exercise could "cure" ME/CFS.

"We designed this pilot study to explore whether the illness was associated with alterations in immunological markers following exercise. Immunological abnormalities are commonly observed in CFS…Concentrations of plasma transforming growth factor-beta (TGF-β) (anti-inflammatory) and tumour necrosis factor-alpha (TNF-α) (pro-inflammatory) have both been shown to be raised*….Abnormal regulation of cytokines may both reflect and cause altered function across a broad range of cell types…..**Altered cytokine levels, whatever their origin, could modify muscle and or neuronal function.***

"Concentrations of TGF-β1 (anti-inflammatory) ***were significantly elevated in CFS patients at all times before and after exercise testing.***

"We found that exercise induced a sustained elevation in the concentration of TNF-α (pro-inflammatory) ***which was still present three days later, and this only occurred in the CFS patients.***

*"**TGF-β was grossly elevated when compared to controls before exercise (and) showed an increase in response to the exercise entailed in getting to the study centre.***

"These data replicate three out of four previous studies finding elevated TGF-β in subjects with CFS.

"The pro-inflammatory cytokine TNF-α is known to be a cause of acute sickness behaviour, characterised by reduced activity related to 'weakness, malaise, listlessness and inability to concentrate', symptoms also notable in CFS.

"These preliminary data suggest that 'ordinary' activity (i.e. that involved in getting up and travelling some distance) may induce anti-inflammatory cytokine release (TGFβ), whereas more intense exercise may induce pro-inflammatory cytokine release (TNF-α) in patients with CFS" (Immunological changes after both exercise and activity in chronic fatigue syndrome: a pilot study. White PD, KE Nye, AJ Pinching et al. JCFS 2004:12 (2):51-66).

2004

"Many patients with (ME)CFS have symptoms that are consistent with an underlying viral or toxic illness. *Because increased neutrophil apoptosis occurs in patients with infection, this study examined whether this phenomenon also occurs in patients with (ME)CFS.* ***Patients with (ME)CFS had higher numbers of apoptotic neutrophils, lower numbers of viable neutrophils, and increased expression of the death receptor, tumour necrosis factor receptor-1 on their neutrophils than did healthy controls. These findings provide new evidence that patients with (ME)CFS have an underlying detectable abnormality in their immune cells****"* (Kennedy G et al. J Clin Pathol 2004:57(8):891-893).

Commenting on this paper, Dr Neil Abbot, Director of Operations at ME Research UK, noted: "*The new paper by Dr Gwen Kennedy (MERGE Research Fellow) and colleagues reports evidence of increased neutrophil apoptosis (programmed cell death) in ME/CFS patients. Neutrophils represent 50-60% of the total circulating white blood cells and are fundamental to the functioning of an intact immune system.* ***The data presented in this report are consistent with the presence of an underlying, detectable abnormality in immune cell behaviour of many ME/CFS patients, consistent with an activated inflammatory process, or a toxic state****"* (Co-Cure RES MED 30th July 2004).

Also commenting on this paper, Dr Charles Shepherd of the UK ME Association said: "*The BMJ doesn't normally show any interest in research which supports a physical cause for ME/CFS. However, today's edition does refer to some*

interesting new findings relating to neutrophil apoptosis (increased cell death involving a particular type of white blood cell) that was reported in the Journal of Clinical Pathology (2004:57:891-893). ***The BMJ goes on to conclude: 'Evidence is emerging that people with chronic fatigue syndrome may have a detectable immunological abnormality'.*** *They may be 15 years behind the rest of us in coming to this conclusion, but better late than never!"* (Co-Cure MED, NOTICE, 20th August 2004).

2004

"The exacerbation of symptoms after exercise differentiates (ME)CFS from several other fatigue-associated disorders. Research data point to an abnormal response to exercise in patients with (ME)CFS compared to healthy sedentary controls, and to an increasing amount of evidence pointing to severe intracellular immune dysregulation in (ME)CFS patients. *The dysregulation of the 2-5A synthetase/RNase L pathway may be related to a channelopathy, capable of initiating both intracellular hypomagnesaemia in skeletal muscles and transient hypoglycaemia.* ***This might explain muscle weakness and the reduction of maximal oxygen uptake, as typically seen in (ME)CFS patients.*** *The activation of the protein kinase R enzyme, a characteristic feature in at least a subset of (ME)CFS patients, might account for the observed excessive nitric oxide (NO) production in patients with (ME)CFS. Elevated NO is known to induce vasodilation, which may cause and enhance post-exercise hypotension"* (J Nijs, K De Meirleir, N McGregor, P Englebienne et al. Med Hypotheses 2004:62(5):759-765).

2004

"Immunological aberration (in ME/CFS) may be associated with an expanding group of neuropeptides and inappropriate immunological memory. ***Vasoactive neuropeptides act as hormones, neurotransmitters, immune modulators and neurotrophes. They are immunogenic and known to be associated with a range of autoimmune conditions. They are widely distributed in the body, particularly in the central, autonomic and peripheral nervous systems and have been identified in the gut, adrenal gland, reproductive organs, vasculature, blood cells and other tissues. They have a vital role in maintaining vascular flow in organs and are potent immune regulators with primary anti-inflammatory activity. They have a significant role in protection of the nervous system (from) toxic assault. This paper provides a biologically plausible mechanism for the development of (ME)CFS based on loss of immunological tolerance to the vasoactive neuropeptides following infection or significant physical exercise. Such an occurrence would have predictably serious consequences resulting from the compromised function of the key roles these substances perform"*** (Staines DR. Med Hypotheses 2004:62(5):646-652).

2004

The November 2004 issue of NeuroImmunoModulation contained the Report of the Research Symposium on ME/CFS convened by the CFIDS Association and co-sponsored by the CDC and the NIH. The report is entitled "Immunologic Aspects of Chronic Fatigue Syndrome" and is important because it sets out the necessary direction of future research.

*"(ME)CFS is a serious health concern …. studies have suggested an involvement of the immune system. A Symposium was organised in October 2001 to explore the….association between immune dysfunction and (ME)CFS, with special emphasis on the interactions between immune dysfunction and abnormalities noted in the neuroendocrine and autonomic nervous systems of individuals with (ME)CFS. This paper represents the consensus of the panel of experts who participated in this meeting….****Data suggest that persons with (ME)CFS manifest changes in immune responses that fall outside normative ranges…(ME)CFS seems to be a multi-system disorder….There is substantial evidence that a large proportion of patients has some immunologic abnormalities, including decreased natural killer cell activity, an increase in the percentage of T cells expressing activation markers, decreased lymphocyte stimulation by certain mitogens and soluble antigens, and increased production of certain pro-inflammatory cytokines. The humoral immune system has also shown frequent abnormalities, including hypergammaglobulinemia, increased titres of*

various antibodies, and the presence of immune complexes. These changes support the conclusion that dysregulation of cellular and humoral response are associated with CFS…..The pattern of immune abnormalities suggests that immunologic factors may contribute to the pathogenesis*….It seems plausible that the over-production of some cytokines contributes to the fatigue. The recent demonstration of activation of the 2-5A synthetase pathway (associated with interferon-α signal transduction) in some (ME)CFS patients provides support for this hypothesis…The search for infectious agents in (ME)CFS patients should be initially guided by…the detection of circulating antibodies and antigens to agents that have been implicated in (ME)CFS….**A good experimental model…should…utilise well-characterised and homogeneous subject populations…. The panel recommends the implementation of longitudinal studies that include the following key elements: well-characterised cases and controls; assays designed to measure immune function: (a) natural killer cell activity; (b) percentage of peripheral blood lymphocytes expressing activation markers; (c) pro-inflammatory cytokines and soluble receptors; (d) Th-1 and Th-2 responses; (e) activity of the 2-5A synthetase pathway, and (f) serum immunoglobulin levels; selected measures of autonomic nervous system and neuroendocrine functioning; functional magnetic resonance imaging studies; studies… to demonstrate the presence or absence of viral/microbial genetic material….The use of interdisciplinary, multi-site (including international) longitudinal studies to explore links between the variations noted in (ME)CFS patients' immune, neuroendocrine, and cardiovascular systems is critical to developing an understanding of relationships among causal factors, symptom progression, and recovery…. Three primary methodological barriers impair the investigations of (ME)CFS: poor study design, the heterogeneity of the CFS population, and the lack of standardised laboratory procedures. The quality of previous CFS research (is hampered by) multiple differences in methods of subject recruitment and classification (and) clinical definitions applied and outcome measures used. It is our obligation to overcome the methodological barriers outlined above***" (Gerrity TR et al. NeuroImmunoModulation 2004:11(6):351-357).

2004

*"**Patients (with ME/CFS) are more likely to have objective abnormalities of the immune system than control subjects**. We measured the frequency of certain HLA antigens (and) restricted our analysis to Class II molecules, as these appear to be more specific predictors of susceptibility to immunologically-based disorders. **The frequency of the HLA-DQ1 antigen was increased in patients compared to controls. This association between (ME)CFS and the HLA-DQ1 antigen translates into a relative risk of 3.2**"* (RS Schacterle, Anthony L Komaroff et al. JCFS 2004:11(4):33-42).

2004

The Seventh Biennial AACFS International Research and Clinical Conference was held on 8th – 10th October 2004 at Maddison, Wisconsin. **It was attended by 120 doctors and 112 patients, and research presenters came from people from about 16 different countries, but Professor Klimas commented that there was no-one from England (in discussion afterwards, she said *"But none from England this year, and I don't know why"*)**. As one attendee put it: "*Her statement was one of dismayed puzzlement…it was spoken by a busy researcher who doesn't have time for politics and is completely baffled why (researchers from the UK) are no longer present at the research symposium…. Probably the most expressive part of Dr Klimas' comment was her non-verbal expression – she was expressing deep and personal concern"* (private communication). As another person observed: "*I was assured by the Department of Health that those running the PACE Trial are international specialists, yet not one of them thought it necessary to attend such an important international conference where the 'immunologic and neurologic malfunctions' of ME/CFS featured so strongly. Doesn't that just say it all?"* (private communication).

Professor Anthony Komaroff (Harvard) began the conference with an over-view of current research, saying that research has shown abnormalities in many systems: "***Studies of immune activation indicate that activated lymphocytes can pass through the blood-brain barrier in small***

numbers…and thereby activate lymphocytic dendritic cells that reside in the brain, particularly microglia and perivascular cells, and this state of low-level activation can last decades. Activated microglia, like macrophages, secrete pro-inflammatory cytokines (e.g. TNFα, IL-1β) and NO (nitric oxide). There is increased neutrophil apoptosis in (ME)CFS".

Professor Robert Suhadolnik (Temple University, Philadelphia) reviewed the evidence and effect of the up-regulated 2-5A synthetase RNase L antiviral defence pathway. **There is a 500-fold excess of bioactive 2-5A in (ME)CFS. The higher the RNase L activity, the lower the patient's ability to function. These patients also have a low molecular weight 37 kDa RNase L which is not found in healthy controls, patients with depression, or fibromyalgia patients. The patient has lowered signal transduction, lowered cell proliferation, lowered ATP production, lowered cellular metabolism, lowered protein synthesis, impaired NK cell function, abnormal exercise response, loss of potassium from muscle, abnormal sodium retention, hyperventilation, central fatigue, sleep disturbances, and muscle cramps and weakness.**

Dr Kevin Maher (University of Miami) **presented evidence that "*key proteins associated with the cytolytic process (granzymes A and B) are present at lower cellular concentrations in NK cells from individuals with (ME)CFS".***

Dr Jo Nijs (Belgium) presented **evidence for an association between intracellular (elastase activity) immune dysregulation and impairments in cardio-respiratory fitness in (ME)CFS patients. This study indicates subtle underlying lung damage.** (A presentation by Dr Anna Garcia-Quintana from Spain showed that **the average maximal oxygen uptake of (ME)CFS patients was only 15.2, whereas the sedentary controls' uptake was 25.9, and the physically active controls' uptake was 66.6**).

Professors Nancy Klimas and Leonard Jason discussed **sub-grouping**, concluding that finding distinct sub-populations has clear clinical implications by defining groups for targeted intervention. Objective measures are needed for this approach and can include issues such as immune disturbance (cytokines, cell function). ***"Sub-grouping is the key to understanding how (ME)CFS begins, how it is maintained, how medical and psychological variables influence its course and how it can be prevented, treated and cured".***

In her summary Professor Klimas noted that all the reports confirmed and augmented the same cycle of immunological and neurological malfunctions but said that there is a risk of (ME)CFS being defined as a behavioural disorder if (biomedical) research is not supported (with grateful acknowledgement to Paula Carnes, Dr Rosamund Vallings and Dr Charles Lapp).

2005

In her Incoming Presidential Address for the AACFS, immunologist Professor Nancy Klimas said: "*I am proud to assume the role of president of the AACFS, an organisation with a pressing and compelling mission. The AACFS exists to promote research, education, and advocacy to further our understanding and eventually develop effective treatments for this disabling illness….**Our patients are terribly ill, misunderstood, and suffer at the hands of a poorly informed medical establishment and society***" (Co-Cure ACT: 21st March 2005).

2005

*"There are a group of diseases that the allergist-immunologist may be called up to manage…that appear to be initiated by allergic mechanisms….In patients with (ME)CFS, there appears to be a fundamental dysfunction of the neuroendocrine-immunological system with deficiencies of immunological and neurological function which, together with chronic viral infection, may lead to a sequence of events responsible for the symptoms of this disorder….**An understanding of the interactive responses involved in the neuroendocrine-immunological network is essential for a comprehension of the pathophysiology of…(ME)CFS…and the role of allergies appears to be an important triggering*

event…" (Bellanti JA et al. Allergy Asthma Proc 2005:26(1):19-28).

2005

*"**Arguments exist as to the cause of (ME)CFS. Some think that it is an example of symptom amplification indicative of psychogenic illness, while our group thinks that some (ME)CFS patients may have brain dysfunction.** We did spinal taps* (lumbar puncture) *on (ME)CFS patients. **We found that significantly more (ME)CFS patients had elevations either in protein levels or numbers of cells than healthy controls and (some) patients had protein levels and cell numbers that were higher than laboratory norms. In addition, of the 11 cytokines detectable in spinal fluid, (some) were lower in patients than in controls (and some) were higher in patients. The results support two hypotheses: that some (ME)CFS patients have a neurological abnormality and that immune dysregulation within the central nervous system may be involved in this process.** A recent study showing elevations of IL-8 and IL-10 levels during chemotherapy-induced symptoms resembling some of those seen in (ME)CFS provides additional evidence for this hypothesis"* (Benjamin H Natelson et al. Clin Diagn Lab Immunol 2005:12(1):52-55).

2005

An article in The Scientist pointed out the need to measure cytokines in diverse disorders: "*The immune system is often likened to the military. The body's army has weapons such as antibodies and complement, and soldiers such as macrophages and natural killer cells. The immune system sports an impressive communications infrastructure in the form of intracellular protein messengers called cytokines and the cellular receptors that recognise them. The cytokine family consists of such soluble growth factors as the interleukins, interferons, and tumour necrosis factor, among others. **Their measurement has become an integral part of both clinical diagnostics and biomedical research**"* (JP Roberts. The Scientist 2005:19:3:30).

It needs to be noted that in the UK, the NICE Clinical Guideline 53 on "CFS" (2007) proscribes such measurements in people with ME/CFS, as did the MRC's "CFS/ME Research Advisory Group Research Strategy" Report of 1st May 2003, as did the CMO's Report of 2002, and as did the Joint Royal Colleges Report (CR54) of 1996.

2005

"Hyperactivation of an unwanted cellular cascade by the immune-related protein RNase L has been linked to reduced exercise capacity in persons with (ME)CFS. This investigation compares exercise capabilities of (ME)CFS patients with deregulation of the RNase L pathway and CFS patients with normal regulation. The results implicate abnormal immune activity in the pathology of exercise intolerance in (ME)CFS and are consistent with a channelopathy involving oxidative stress and nitric-oxide toxicity" (Snell CR et al. In Vivo 2005:19(2):387-390).

2005

*"**Diminished NK cell cytotoxicity is a frequently reported finding (in ME/CFS**). However, the molecular basis of this defect has not been described. Perforin is a protein found within intracellular granules of NK and cytotoxic T cells. **Quantitative fluorescence flow cytometry was used to the intracellular perforin content in (ME)CFS subjects and healthy controls. A significant reduction in the NK cell associated perforin levels in samples from (ME)CFS patients compared to healthy controls was observed. There was also an indication of a reduced perforin level within the cytotoxic T cells of (ME)CFS subjects, providing the first evidence (of) a T cell associated cytotoxic deficit in (ME)CFS. Because perforin is important in immune surveillance and homeostatis of the immune system, its deficiency may prove to be an important factor in the pathogenesis of (ME)CFS and its analysis may prove useful as a biomarker in the study of (ME)CFS"*** (Maher KJ, Klimas NG, Fletcher MA. Clin Exp Immunol 2005:142(3):505-511).

2005

"Previous research has shown that patients with (ME)CFS present with an abnormal exercise response and exacerbations of symptoms after

physical activity. The highly heterogeneous nature of the CFS population and the lack of uniformity in both diagnostic criteria and exercise testing protocols preclude pooling of data. Still, we conclude that at least a subgroup of CFS patients present with an abnormal response to exercise. Importantly, the exacerbation of symptoms after exercise is seen only in the (ME)CFS population and not in fatigue-associated disorders such as depression*. Earlier (studies) revealed that in (ME)CFS patients, irrational fear of movement is not related to exercise performance.* ***The aim of this study was to examine the interactions between several intracellular immune variables and exercise performance in (ME)CFS. These data add to the body of literature showing impairment of intracellular immunity in patients with (ME)CFS. The results provide evidence for an association between intracellular immune dysregulation and exercise performance in patients with (ME)CFS"*** (J Nijs, N McGregor, K De Meirleir et al. Medicine & Science in Sports & Exercise 2005:Exercise Immunology in CFS:1647-1654).

2005

"The hypothesis of the present study is that the appearance of cell-specific autoimmune antibodies may define subsets of (ME)CFS. ***(ME)CFS is clinically similar to several autoimmune disorders that can be diagnosed and characterised by autoantibody profiles****. For this reason, we conducted an exhaustive evaluation of 11 ubiquitous nuclear and cellular autoantigens in addition to two neuronal specific antigens. Very few studies have evaluated the presence of autoantibodies in people with (ME)CFS. The findings of this study hint that evaluation of certain autoantibodies may give clues to on-going pathology in subsets of (ME)CFS subjects.* ***Among (ME)CFS subjects, those who had been sick longer had higher rates of autoantibodies****"* (S Vernon et al. Journal of Autoimmune Diseases May 25th, 2005:2:5).

2006

The CFIDS Association produced a special issue of the Chronicle entitled "The Science and Research of CFS" (2005-2006); it contained a major article by Professor Nancy Klimas entitled "The State of CFS Research" in which she noted **factors that have contributed to the slow progress in unravelling (ME)CFS: these included the troublesome case definition, the need to identify sub-groups and the need to attract good researchers**. Professor Anthony Komaroff considered the known abnormalities of the neurological and immune systems, and **Dr Susan Levine provided a detailed overview of the immune abnormalities in her article entitled "Immune System Gone Haywire?" in which she focused in the six prominent immune abnormalities consistently shown over the previous 18 years**: (i) impaired function of NK cells; (ii) increased number of destructive T cells and increased number of T cells expressing activation markers; (iii) activation of several pro-inflammatory cytokines; (iv) dysregulation of the 2'5 A RNase L antiviral pathway; (v) predominance of Th-2 cellular immunity and (vi) differential expression of gene markers whose products cause T cell activation**. She noted that these findings are important and intriguing, in particular that intracellular perforin, an NK-cell lytic protein, is reduced in (ME)CFS patients. She noted that in (ME)CFS there is often reactivation of latent viruses and she also drew attention to the observation of aberrant cytotoxicity in (ME)CFS subjects who demonstrated a differential gene expression of at least 35 gene sequences compared with matched normal controls that suggest a link with organophosphate exposure. In addition, she noted that stress is known to affect both immune activity and neuroendocrine responses in (ME)CFS.**

2006

In an article entitled "Exploring the Gene Scene", Dr Jonathan Kerr from St George's University of London said: "*In 2001 I became increasingly involved in a collaborative study group concerned about the lack of research attention (ME)CFS has received, particularly in terms of how the disease is actually caused and perpetuated.* ***We also take issue with the trivialisation of (ME)CFS and the labelling of patients as sufferers of a psychiatric or psychological disease. To address the problem, we turned to the study of gene activity……****Most genes are expressed in the white blood cells and various groups have shown that the white blood cells of (ME)CFS patients exhibit reproducible*

*alterations in gene expression as compared with normal controls….**Certain themes of gene activity are emerging, of which 'immunity and defence' is the most prominent. This supports previous findings on the role of the immune system in the maintenance of this disease….16 genes were shown to be expressed at very different levels in the (ME)CFS cases compared with the controls. These differentially expressed genes were involved in several processes, including the immune response, the mitochondria (or powerhouse of the cell), conversion of DNA to RNA (termed transcription) and conversion of RNA to protein (termed translation). Although this indicates a complex picture, it's proof that (ME)CFS patients exhibit significant and reproducible differences in gene expression compared with controls….Knowledge of how a disease is caused can lead directly to design and utilisation of treatments to correct the abnormal processes, which can eventually lead to improvement or cure of the disease***" (The CFIDS Chronicle, Spring 2006:8-11).

2006

At the Invest in ME Conference held on 12th May 2006 in London, expert speakers presented their work, **including evidence from Dr Jonathan Kerr from St George's University, London, that most of the abnormally expressed genes seen in (ME)CFS are involved in the immune system**.

The take-home message was:

- ***Since a prolonged inflammation is at the heart of this condition, all speakers advocated the use of the term Myalgic Encephalomyelitis, not Chronic Fatigue Syndrome, since most if not all illnesses cause 'fatigue'***

- ***Inflammation is at the heart of ME – the immune system response is indicative of inflammation; inflammation is in the muscles and in the blood vessels***

- ***The illness is not and never has been 'all in the mind'***

- ***There is a genetic predisposition for ME***

- ***ME is a legitimate physical illness and patients are really ill – their immune, endocrine and neurological systems are compromised and they should not be made to exercise***

- ***The truth about ME is already out there, so why does widespread ignorance and mis-information remain?*** (Co-Cure ACT; 17th May 2006).

2006

*"**The diagnostic criteria of CFS define a heterogeneous population composed of several subgroups. This study was designed to examine NK cell activity as a potential subgroup biomarker. The results (provide) evidence in support of using NK cell activity as an immunological subgroup marker in (ME)CFS. Improved treatment options will only come with better understanding of the syndrome's underlying pathophysiology. The present study specifically investigated the existence of an immunological subgroup of CFS patients.*** Reduced NK cell activity may contribute to enhanced cytokine production. ***Given the role that NK cells play in targeting virally infected cells, a clinically significant reduction in NK cell activity may lead to activation of latent viruses and new viral infections. (ME)CFS is a misunderstood condition. Research in the last two decades has produced little advancement in the understanding of the pathophysiology of (ME)CFS. Unfortunately, this lack of progress seems to have further contributed to the belief among some members of the medical community that (ME)CFS is not an actual organic condition"*** (Scott D Siegel, Mary Ann Fletcher, Nancy Klimas et al. J Psychosom Res 2006:60:6:559-566).

2006

"(ME)CFS is a poorly defined medical condition which involves inflammatory and immune activation. The Type I interferon antiviral pathway has been repeatedly shown to be activated in the most afflicted patients. An abnormal truncated form of ribonuclease L (37-kDa RNase L) is also found in (ME)CFS patients

and this protein has been proposed as a biological marker for (ME)CFS. The levels of this abnormal protein have been significantly correlated to the extent of inflammatory symptoms displayed by (ME)CFS patients" (M Fremont, K De Meirleir et al. JCFS 2006:13(4):17-28).

2006

In a study of cytokine genomic polymorphisms in (ME)CFS, Italian researchers found *"a highly significant increase in TNF-857 and CT genotypes among patients with respect to controls and a significant decrease of IFN gamma low producers among patients with respect to controls…**We hypothesise that (ME)CFS patients can have a genetic predisposition to an immunomodulatory response of an inflammatory nature probably secondary to one or more environmental insults"***

(N Carlo-Stella et al. Clin Exp Rheumatol 2006:24(2):179-182).

2006

On 8th September 2006 Professors Nancy Klimas and Mary Ann Fletcher attended a "Questions and Answers" Patient Session in Wellington, New Zealand at which **Professor Klimas said she proves (ME)CFS disability by carrying out laboratory testing with Immune Activation Panels: (DR, CD26 expression, Th2 cytokine shift, pro-inflammatory cytokine expression TNFα, IL-1 and IL-6) and evidence of functional defects (NK cell dysfunction, CD8 abnormalities, decreased perforin, granzymes, macrophage abnormalities and antibody production).** When asked if these were available in New Zealand, she replied*: "Putting panels together shouldn't be a problem. These kinds of tests are not routine, but they should be do-able by immunologists"*. When then asked: "*Given the evidence of an inflammatory response, wasn't the old name ME better than CFS?"*, to which she replied: *"Sure, ME is a much better name. The problem is that we've fought so hard in the US to get recognition as CFS (because) there is a Social Security ruling under that name, that changing it now would cause a lot of issues. I'm just trying to get slash (/) ME into it".* **She was then asked why there was a Th-2 shift and she replied: "*By measuring the number of Type 1 lymphocyte cells and comparing them to Type 2 lymphocytes, we find more of Type 2. We also find fewer numbers and poorer functioning NK cells which is an outcome of this shift. We proved that this was implicated in the symptomatology of the illness by the self-autologous infusion experiment where people were re-infused with the corrected ratio and their symptoms improved….Why the immune response is being pushed this way is at the heart of the cause of the illness"***. She was then asked: **"*What are the consequences of this Type 2 shift?"* to which she replied: "*A lot of pro-inflammatory immune activation is not held in check and this gives rise to a host of symptoms"***. Professor Fletcher was asked if people with ME/CFS should give blood, and she replied: *"No, I don't think it's a good idea for two reasons – (a) most patients are 1 litre low in blood (most of Dr Klimas' patients have around 3.5 L instead of 4.5 L, so why would you want to take out another litre?); (b) to my mind there are no studies to prove that ME is not infectious, so we can't say with complete certainty that an infection will not be passed on"* (Co-Cure MED 8th December 2006).

2006

On 3rd November 2006 the US Centres for Disease Control (CDC) announced its "CFS Toolkit" to inform not just the US but the whole world about the nature and severity of ME/CFS. The following are extracts from the Press Conference:

Dr Julie Gerberding, Director of the US CDC: *"One of the things that CDC hopes to do is to help patients know that they have an illness that requires medical attention, but also to help clinicians be able to understand, diagnose and help people with the illness.* ***But more importantly, to be able to validate and understand the incredible suffering that many patients and their families experience in this context****. We are committed to improving the awareness that this is a real illness and that people need real medical care and they deserve the best possible help that we can provide.* ***The science has progressed (which has) helped us define the magnitude and understand better the clinical manifestations (and this has) led to a sorely needed foundation for the recognition of the underlying biological aspects of the illness****. We need to respect and make that science more*

visible. I have heard from hundreds and hundreds of people who are telling their stories – their courage, their commitment to try to live the best possible life they can (and) the tremendous impact that this is having on their ability to function".

Dr William Reeves, Chief of Chronic Viral Diseases Branch at CDC: ***"We've documented, as have others, that the level of impairment in people who suffer from (ME)CFS is comparable to multiple sclerosis, AIDS, end-stage renal failure, chronic obstructive pulmonary disease. The disability is equivalent to that of some well-known, very severe medical conditions. We found that (ME)CFS follows a pattern of remitting and relapsing symptoms, the symptoms can change over time, and that spontaneous recovery is rare. We found that the best predictor for (ME)CFS was intensity of the initial infectious disease. The sicker the patient when s/he first got infected, the more likely they were to have persisting chronic symptoms. There were no other factors, psychological or biological, that held up under thorough analysis".***

Professor Anthony Komaroff, Harvard Medical School: *"**There are now over 4,000 published studies that show underlying biological abnormalities in patients with this illness. It's not an illness that people can simply imagine that they have and it's not a psychological illness. In my view, that debate, which was waged for 20 years, should now be over.** A whole bunch of studies show that the hormone system is different in patients with (ME)CFS than in healthy people, people with depression and other diseases**. Brain imaging studies have shown inflammation, reduced blood flow and impaired cellular function in different locations of the brain. Many studies have found that the immune system appears to be in a state of chronic activation (and) genes that control the activation of the immune system are abnormally expressed in patients with this illness.** A number of studies have shown that there probably are abnormalities of energy metabolism in patients with this illness".*

Professor Nancy Klimas, Professor of Medicine, University of Miami: *"I've treated over 2,000 (ME)CFS patients. Today, **there is evidence of the biological underpinnings. And there's evidence that the patients with this illness experience a level of disability that's equal to that of patients with late-stage AIDS, patients undergoing chemotherapy, patients with multiple sclerosis**. And that has certainly given it a level of credibility that should be easily understood. **There are diagnostic criteria that enable clinicians to diagnose (ME)CFS in the primary care setting".***

The full Press Conference is available at: http://www.cdc.gov/media/transcripts/t061103.htm

2006

Commenting on a study in the November 2006 issue of Archives of General Psychiatry (Childhood Trauma Ups the Risk of Chronic Fatigue Syndrome), Professor Nancy Klimas said: "*We're not talking about a bunch of stressed-out people. **We're talking about the biological underpinnings of a real and very debilitating illness. We're trying to remove the stigma of a psychiatric overlay and put it back in biology, where it belongs…..It's important to see that CFS has subgroups. It's really important not to merge all these observations into one solid, big group***" (Co-Cure Res 8th November 2006).

2006

In the press follow-up of the CDC Toolkit launch, on 24th November 2006 Professor Nancy Klimas said that research over the past 20 years was beginning to figure out the biological underpinnings of the syndrome, which she thinks is badly misnamed: "***If it were called chronic neuroinflammatory disease, then people would get it. Up until now nobody's been willing to change the name, but now there's proof that inflammation occurs in the brain. There's evidence that the patients with this illness experience a level of disability that's equal to that of patients with late-stage AIDS, patients undergoing chemotherapy (and) patients with multiple sclerosis***". She and other investigators have shown that different types of cells within the immune system are abnormal either in number or function (Co-Cure ACT 25th November 2006).

2007

The 8th International Association of Chronic Fatigue Syndrome (IACFS, formerly the AACFS) Conference was held at Fort Lauderdale, Florida, from 10th-14th January 2007. The following notes are taken from published reports of conference attendees (including Professor Charles Lapp, Dr David Bell, Dr Rosamund Vallings, Dr Lesley Ann Fein, Virginia Teague, Pat Fero, Cort Johnson, John Herd and Pamela Young, whose various reports are on the internet), to whom grateful acknowledgment is made.

The conference was attended by over 250 clinicians and researchers from 28 different countries and there was a strong sense that they were all co-operating to build on the science, and that it is **the science that has freed the world from any doubt that ME/CFS is a legitimate disease with an aetiology that is not rooted in the psyche. It was described as "*this miserable illness*".**

One of the most striking elements was the convergence of research findings: the three areas that came up again and again were inflammation, mitochondrial abnormalities, and vascular problems.

There was a significant confluence of findings on (i) elastase (a protease enzyme which digests and degrades a number of proteins, including elastin, a substance that supports the structural framework of the lungs and other organs); (ii) vascular problems; (iii) apoptosis (programmed cell death); (iv) free radical production (highly damaging to DNA, to cell membranes and to proteins); and (v) the presence of inflammation in ME/CFS.

In ME/CFS, testing for elastase, RNase-L, C-reactive protein, selected cytokines and NK cell activity are recommended because they are objective markers of pathophysiology and severity.

The importance of sub-tying was recognised and emphasised.

There are elevated pro-inflammatory cytokines (immunologically-based chemicals that can cause viral symptoms) in patients with ME/CFS.

Dr Brian Gurbaxani and Dr Suzanne Vernon et al (CDC, Atlanta) demonstrated that **increased levels of IL-6 correlate well with C-reactive protein (CRP) and are proportionate to symptom severity in ME/CFS.**

Dr Barry Hurwitz from the University of Miami showed that **pro-inflammatory cytokines have a secondary effect in reducing red blood cell (RBC) volume, due to probable suppression of RBC production in the bone marrow.**

Professor Mary Ann Fletcher, a colleague of Professor Nancy Klimas from the University of Miami, found that **perforin (a molecule in cytotoxic lymphocytes) is low in ME/CFS, as are NK cells.**

Anthony Komaroff (Professor of Medicine, Harvard) **summarised the immune abnormalities that have been demonstrated in ME/CFS. These include activated CD8 (T cells); poorly functioning NK cells; novel findings – seen only in ME/CFS -- of abnormalities of the 2-5A pathway (RNase-L ratio); cytokine abnormalities (pro-inflammatory dysregulation); increased TGF, and 27 times more circulating immune complexes than in controls.**

Other areas of abnormality seen in ME/CFS that were addressed at this conference included the cardiovascular system (especially the evidence of microvascular inflammatory problems and arterial stiffening; the evidence that 70% of people with ME/CFS have a low red blood cell volume; the low cardiac index of ME/CFS patients, this being so severe that it falls between the value of patients with myocardial infarction and those in shock, and inverted T waves), brain imaging (especially the evidence of reduced blood flow to the brain including the area responsible for the autonomic nervous system; the evidence of reduced grey matter volume, and the evidence of arteriolar vasculopathy or a blood vessel disease described as a "*systemic mico-vascular inflammatory process*", a process that would affect not only the brain but every organ system in the body), proteomics (the "*unbelievable*" finding of unique markers in the cerebrospinal fluid of ME/CFS patients that are completely absent from the control group, and the finding of one protein – keratin – that is associated with inflammation of membranes covering the brain and spinal cord),

evidence of persisting viral activity, gastrointestinal dysfunction, sleep disruption, pain, cognitive impairment, neuroendocrine dysfunction, genomics (especially the findings of three main abnormalities in ME/CFS, involving the immune system, mitochondrial function and G-protein signalling: of seven genes up-regulated in ME/CFS, three in particular are notable, these being gelsolin that is involved in apoptosis, one that is upregulated by organophosphates, and the other being a mitochondrial gene that is involved in the demyelination of nerves), and paediatric issues. This conference highlighted the difference between psychiatry and science (http://www.meactionuk.org.uk/Facts_from_Florida.htm).

2007

On 25th May 2007 the charity ME Research UK (MERUK) hosted an International Research Conference at the Edinburgh Conference Centre, Heriot Watt University, Edinburgh. There were six keynote lectures and eight presentations, with several Question & Answer sessions. The following notes are taken from the keynote lectures and presentations. Items relating to the immunology of ME/CFS include the following:

Presentation by Mark Robinson (Department of Applied Physiology, University of Strathclyde): "Response of plasma cytokine IL-6 and its receptors to exercise in ME/CFS"

"The physiological role of IL-6 has classically been studied in the context of the immune response, since it is able to exert both pro- and anti-inflammatory activities. More recently, IL-6 has been of keen interest to exercise physiologists, with the observation that, even without skeletal muscle damage, plasma levels of this cytokine increase dramatically. In 2000 (researchers) demonstrated that the source of this increased IL-6 can almost exclusively be attributed to the working of skeletal muscle, where it is both produced and subsequently released".

"Exercise-induced IL-6 in the muscle acts in a hormone-like manner, helping to maintain the fuel homeostasis during exercise and when skeletal muscle glycogen levels become depleted".

"The main finding of the study was a clear trend towards a lower resting level of the soluble IL-6 receptor in ME/CFS patients".

Keynote Lecture by Professor Nancy Klimas (University of Miami): "The Immunology of ME/CFS".

Nancy Klimas, Professor of Medicine & Immunology at the University of Miami and world-renowned expert on the immunology of ME/CFS, delivered a compelling keynote lecture. She said **there is a real genetic component in ME/CFS (HLA-DR, which predisposes to autoimmune illness).** She stressed the findings of an Australian study which found that the severity of the initial infection is the single predictor of perpetuation of ME/CFS and that **there is no psychological component in its perpetuation.**

Professor Klimas explained the imbalance seen in ME/CFS between Type I and Type II cytokines: **in ME/CFS they see a lot of Type II cytokine expression, which means there is an inhibition of Type I expression, which in turn triggers the inflammatory cascade of tumour necrosis factor (TNF), IL-6 and IL-1. This is important, because Type I cytokines are needed for the function of cytolytic T cells and NK cells are part of the whole immune mechanism, which is being inhibited in ME/CFS.**

She pointed out that what has been seen over many years of research by many different groups is (quote) *"a lot of evidence of this chronic immune activation, looking at expression of activation markers on the cells, looking at cytokine levels, looking at cytokine expression.* ***The consequence, or may be a part of this, is a lot of functional abnormalities of cytotoxic T cells and NK cells, macrophage abnormalities, antibody production abnormalities and neutrophil abnormalities. NK cell function is very poor—NK cells should kill in a certain unit of time: in normals this is 30-40% in four hours, but in ME/CFS it is half of that".***

Professor Klimas said **the most important thing that has come out of her group recently is the discovery of very low perforin (which she described as "*the killing stuff of the cell*"). She said that very low perforin levels in the cytotoxic T cell matters, because the anti-viral defence is impaired. In ME/CFS the perforin is half what it should be.**

She emphasised that in addition to poor cell function, the cells are very activated and very stimulated, and there are consequences of an activated cell – what is seen is not only *"this big immune activation, but apoptosis – a lot of cell death"*, resulting in a constant drive to make more cells, especially neutrophils and lymphocytes. Thus there is "*a constant drive to keep the system in overdrive in trying to keep up with cell loss".*

Her group has also seen a CD26 cell receptor in ME/CFS – this is seen in an activated cell, and the number of cells expressing this receptor is elevated, even though there are fewer molecules per cell. This matters, because the number of these activated receptors on the cell determines the function of that cell (which cannot "*activate up"* the function).

Professor Klimas summarised all this as (i) an over-activated system; (ii) a system that is not functional and (iii) what she described as "*the stuff of the cell – the thing you need to make the cell function well – being under-produced".*

She then spoke about neuropeptide Y, which is a very important neuropeptide of interest to the vascular biologists' findings in ME/CFS. It has a large number of regulatory functions, including the immune system and the autonomic system. **It is a biomarker. They looked at more than 100 patients and found a significant difference between ME/CFS patients and controls. Professor Klimas said this is important.**

She went on to speak about clinical correlates: **they had found that people who had low cognitive difficulties had good T cell function but people who had very high cognitive difficulties had the poorest T cell function, so there is a definite clinical correlate. This correlate has also been shown with NK cells, and once again she emphasised that this immune connection matters.**

She discussed the fact that genomics have put some focus on the HPA axis dysregulation and said that IL-6 is associated with the intensity of that dysregulation.

She mentioned the role of infection, saying she herself had needed to be convinced about the role of viruses and it was the work of Dr Peterson that had convinced her. **Peterson had shown transmissible living virus in spinal fluid cultures of ME/CFS patients (which definitely should not be there): *"You should not be able to culture anything out of anybody's spinal fluid in the way of a virus or bacteria or anything – it's not OK. That was impressive".***

Professor Klimas went on to talk about enteroviruses in ME/CFS: ***"Enteroviruses keep reappearing – they keep coming back (into the picture). Most recently at our conference in January (the IACFS/ME conference in Florida), Dr Chia from Los Angeles had looked at more than 100 intestinal biopsies (and showed) slide and slide after slide with enteroviruses – it was phenomenal".*** She said that people had previously looked at enteroviruses in muscle, but *"looking at the intestine was a place no-one had ever looked before, and yet the intestine is, beyond the skin, the second biggest immune system component you have, and a tremendous place to have a lot of antigen exposure and a good reason to have chronic immune activation".*

She then pointed out that the genomics work is very exciting as applied to immunology and virology, as it replicates the immune data by a completely different method.

Professor Klimas began her lecture by saying: "*People are finding things that fit. This all makes sense. It's a very exciting time because the puzzle*

we've talked about all these years is really fleshing out into a real picture".

She concluded by conveying her own enthusiasm, saying that due to new techniques that were not available even five years ago, "*there's been tremendous progress*" and that both patients and investigators should be heartened.

In the Question & Answer session, in response to a question from the floor, Professor Klimas said *"What subgroup do people fit in? What we're down to now is looking for the biological markers that put people in the proper group to give us targeted treatment approaches that make sense for that individual – certainly that's the way, thank goodness, the field is finally moving".* (It must be stressed that this is in direct contrast to the Wessely School, who are intent on collating all states of medically unexplained "fatigue" and rolling out "cognitive restructuring" across the board of "fatigue").

2007

"For decades, (ME)CFS patients were – and still are – dismissed as lazybones or hypochondriacs. ***Many medical doctors and insurance companies still assert that (ME)CFS is a mental condition. The mainstream treatment for (ME)CFS is CBT, which means that patients with (ME)CFS are being treated as having a mental illness with 'treatments' that do not treat any underlying cause. Doctors who treat (ME)CFS patients as suffering from an organic disorder and scientists who examine the biological causes of (ME) are often considered quacks by their colleagues (and) insurance companies, which are sometimes even officially supported by governments in their attempts to eliminate the scientific view that (ME)CFS is an organic disorder.*** *The official acceptance of the latter obviously would mean that the national health care systems are obliged to financially support those patients who are now considered hypochondriacs and, therefore, may easily be suspended from the national health care systems.* ***There is, however, evidence that (ME)CFS is a severe immune disorder with inflammatory reactions and increased oxidative stress. Maes et al show that patients with (ME)CFS show very high levels of nuclear factor kappa beta in their immune cells. NFkβ is the major mechanism which regulates inflammation and oxidative stress. Thus, the increased production of NFkβ in the white blood cells of patients with (ME)CFS is the cause of the inflammation and oxidative stress (seen) in (ME)CFS"*** (Maes et al. Neuroendocrinology Letters, 2007. http://www.michaelmaes.com/).

2007

"Recent research has evaluated genetic signatures, described biologic subgroups, and suggested potential targeted treatments. ***Acute viral infection studies found that initial infection severity was the single best predictor of persistent fatigue****…. Studies of immune dysfunction (have) extended observations of natural killer cytotoxic cell dysfunction of the cytotoxic T cell through quantitative evaluation of intracellular perforin and granzymes. Other research has focused on a subgroup of patients with reactivated viral infection….* ***Our expanded understanding of the genomics of (ME)CFS has reinforced the evidence that the illness is rooted in a biologic pathogenesis that involves cellular dysfunction and interactions between the physiologic stress response and inflammation…. A large body of evidence links (ME)CFS to a persistent viral infection…. (ME)CFS patients exhibited a distinct immune profile compared with fatigued and non-fatigued individuals. These patients displayed increased anti-inflammatory cytokines (IL-10, decreased IFN-γ/IL-10 ratio) and reductions in pro-inflammatory cytokines (IL-6, tumour necrosis factor-α)…****Investigators noted the tropism with brain and muscle and suggested that the neuroinflammation seen in neuroimaging studies of a subgroup of CFS patients may result from enteroviral infection….* ***The clinical implications are consistent with an immune system that may allow viral reactivation and raises a concern for tumour surveillance as well…. The preponderance of available research confirms that immune dysregulation is a primary characteristic of (ME)CFS.*** *Advances in the field should result in targeted therapies that impact immune function, hypothalamic-pituitary-adrenal axis regulation, and persistent viral reactivation in (ME)CFS patients"* (Nancy G Klimas et al. Current Rheumatology Reports 2007:9:6:482-487).

2007

"Understanding how non-pharmacologic interventions differentially affect the subgroups of patients with CFS might provide insights into the pathophysiology of this illness….Baseline measures of normal versus abnormal cortisol were compared on a variety of immune markers….Subgroups of individuals with CFS may react differently to exercise than healthy controls*….Early researchers describing non-pharmacologic behavioural interventions for CFS reported high levels of success (Deale, Chalder, Marks & Wessely, 1997;…Sharpe et al 1996), but more recent studies have had somewhat more mixed results….* ***Those individuals with most impaired HPA axis function might be least able to improve with non-pharmacologic interventions….Jeres, Cleare, Wessely, Wood and Taylor (2005) have confirmed that mean cortisol levels are significantly lower for individuals with CFS when compared with controls across the entire 24-hour span….Many studies do show that CFS is characterised by hypocortisolemia…It is possible that some individuals with CFS have a cortisol deficiency and others do not, but when all are combined into one large CFS category, these important differences are ignored….****Immunologic abnormalities have frequently been reported in the CFS literature…(a) poor cellular function, with low natural killer cell (NKC) cytotoxicity and frequent immunoglobulin deficiencies (most often IgG1 and IgG3) and (b) elevations of activated T lymphocytes, including cytotoxic T cells, and elevations of circulating cytokines….The results of one study found that immunologic functioning did not improve as a result of CBT (Peakman, Deale, Wessely et al, 1997); however, that study did not subgroup according to baseline cortisol findings….****In (our) study, baseline measures of normal versus abnormal cortisol were compared on a variety of immune markers….The results of this study demonstrate that….individuals with normal baseline cortisol levels exhibited the most improvement….This indicates that those who are most impaired on HPA functioning might be least able to improve when provided with non-pharmacologic interventions….****There were significant time and interaction effects of the CD45RA-CD62L- subsets. The normal cortisol group experienced decreasing levels of this subset over the intervention, whereas the abnormal group underwent a significant expansion. This effector subset has been shown in healthy subjects to express high levels of β1 and β2 integrins that are required for homing to inflamed tissues and produce perforin and high levels of IL-4, IL-5 and IFNγ….The continued expansion of this subset in the abnormal cortisol group suggests that a stimulus, present in these individuals but absent in the normal cortisol group, is responsible for driving the proliferation….* ***The modulation of these effector subsets in distinctly different directions, that are associated with HPA axis abnormalities and efficacy of CBT, likely represents an important component of the immune dysfunction associated with the pathogenetic process of CFS…. In summary, subgroups of individuals with either normal or abnormal cortisol levels exhibited different outcomes in a non-pharmacologic treatment trial….This suggests that cortisol levels may serve as an important marker for individuals with CFS that might benefit from non-pharmacologic interventions such as cognitive behavioural therapies****"*
(Leonard A Jason, Mary Ann Fletcher et al. JCFS 2007:14(4):39-59).

2008

In January 2008 the CFIDS Association of America produced a special publication entitled "Defining Moments – 20 years of making CFS history", the key message being that "*Scientific research…has provided incontrovertible evidence that CFS is one of the most complex and widespread illnesses of our time, and that there is a sound scientific basis for the biological origins of the disease (but) many physicians are still incredibly resistant to treating CFS"*.

Professor Nancy Klimas wrote: *"Over the years, people have often asked me if CFS is an immune disorder, a brain disease or a dysfunction of the endocrine system….As an immunologist, I once would have said CFS is clearly an immune dysfunction state, while an endocrinologist would call attention to the adrenal glands irregularities, and a specialist in the autonomic nervous system would be convinced CFS is all about blood pressure abnormalities. Given what we've discovered about the illness, I now tell people CFS is all of these things. We know that (ME) chronic fatigue syndrome has identifiable biologic underpinnings*

because we now have research documenting a number of pathophysiologic processes involving the brain, the immune system, the neuroendocrine system and the autonomic nervous system".

Professor Anthony Komaroff from Harvard wrote: "*Today we have powerful new research technologies… Newer molecular biology technologies allow us to study gene activity inside circulating immune system cells and to look for infectious agents with an accuracy that wasn't possible two decades ago".*

2008

On 6th May 2008 the charity ME Research UK (MERUK) hosted an International Conference on ME/CFS Biomedical Research at the Wellcome Trust Conference Centre, Cambridge ("New Horizons 2008"), at which Professor Nancy Klimas from the University of Miami gave the first Keynote Lecture which was entitled "Clinical Aspects of ME/CFS". **Her emphasis was on the need to assess patients by sub-grouping on the basis of clinical tests and symptom clusters as outlined in the 2003 Canadian Consensus Definition**, of which she was a co-author. **In her view, the post-exertional nature of the symptoms is key. She described her model for the development of the disease and reviewed the chronic immune dysfunction**; she also reviewed the evidence for viral persistence and reactivation before discussing the evidence for endocrine dysfunction such as reduced cortisol output. She noted that gene expression microarray data has become a highly productive tool, mentioning recent studies showing the differential expression of 35 genes for T-cell activation, neuronal and mitochondrial regulatory abnormalities. **She particularly noted that pre-and post exercise challenge studies have indicated differences in genes that regulate ion transport and intracellular functions, saying it may be that evaluation of gene expression profiles will allow pathophysiologic sub-grouping of patients that could result in targeted therapies to impact immune function** (with acknowledgement to Dr Neil Abbot).

2008

On 23rd May 2008 the charity Invest in ME held its third International Conference on ME in London; it was attended by about 165 people including health care professionals and patients.

Dr Jonathan Kerr (St George's University, London) spoke on "Gene Expression in ME/CFS: A Means of Subtyping". **His team looked at a microarray of 47,000 genes from ME/CFS patients and controls taken from normal blood donors. Genes showing differential expression were further analysed using real-time PCR. 13 transcription factors were over-represented and differential expression was confirmed in 88 genes, these being associated with haematological and immunological diseases and function, cancer, apoptosis, immune responses and infections. Graphs showed hugely different results in ME/CFS patients compared with controls** (with acknowledgement to Doris Jones MSc).

2008

*"CFS is an incapacitating illness….**The benefit of classifying individuals with CFS into diagnostic categories is that it facilitates selection of treatment methods**, predictions of response to treatment and communication among clinicians and researchers….**Evidence for multiple immunological abnormalities in CFS have frequently been reported in the literature….People with CFS appear to have two basic problems with immune function: 1) poor cellular function, with low natural killer cell cytotoxicity and frequent immunoglobulin deficiencies (most often IgG1 and IgG3), and b) elevations of activated T lymphocytes, including cytotoxic T cells, and elevations of circulating cytokines. Natelson et al*** (Spinal fluid abnormalities in patients with chronic fatigue syndrome, 2005) ***found increases in cytokines (IL-8 in some patients and IL-10 in others), and these findings support the hypothesis that in some patients with CFS, symptoms may be due to immune dysfunction within the central nervous system….If there are distinct subgroups, then treatment might need to be tailored to the differential needs of patients….Several studies suggest that subgroups of patients with CFS react differently to exercise than healthy controls….In (our) study we examined baseline measures involving immune function… for those who*

improved and those who did not improve following exposure to non-pharmacologic interventions….*Past research has shown that CFS is associated with a shift toward a Type 2 immune response, and in the present study, those with this pattern tended not to improve….In other wards, a dominance of the Type 2 over Type 1 immune response, as indicated by the patterns of lymphocytes subset distributions among those with CFS, did not improve over time….**The current study further supports the contention that clinically distinct subsets of patients within the current definition of CFS….Such differences…highlight the need to define clinical subsets in CFS….Subgrouping is the key to understanding how CFS begins (and) how it is maintained"*** (Leonard A Jason, Mary Ann Fletcher et al. Tropical Medicine and Health 2008: 36:1:23-32).

2008

*"The main hypotheses include altered central nervous system functioning resulting from an abnormal immune response against a common antigen….This review discusses the immunological aspects of (ME)CFS and offers an immunological hypothesis for the disease process….Present data from various sources support the model that (ME)CFS has a propensity to over-produce pro-inflammatory cytokines, coupled with a misregulation of anti-inflammatory cytokines….**These immunological findings show that patients with (ME)CFS may have an infection and that the immune system is chronically activated in response. Several of the differentially expressed genes are related to immunological functions and implicate immune dysfunction in the pathophysiology of the disease**"* (Lorenzo Lorusso et al. Autoimmunity Reviews 2008: doi:10.1016/j.autrev2008.08.003).

2008

"(ME)CFS is a neuro-immune disorder linked to chronic immune activation and dysregulation of the HPA axis….Upsets in immune demographics are reflected in cell-cell signalling and elevated levels of pro-inflammatory cytokines such as INF-α and TNF-α in (ME)CFS. *The HPA axis is central in modulating this inflammatory response through the synthesis of cortisol via a cascade involving adrenocorticotrophic hormone (ACTH) and corticotropin-releasing hormone (CRH)….Accordingly HPA axis dynamics are tightly coupled with those of the immune system….(**ME)CFS patients inhabit a stable hypocortisolic state highly conducive to the emergence of chronic inflammatory immune signalling….The reported changes in connectivity of immune functional nodes align well with observations of altered immune activity in (ME)CFS….We have successfully constructed association networks demonstrating the key role of immune function in (ME)CFS"*** (Jim Fuite, Suzanne D Vernon, Gordon Broderick. Genomics 2008:92:6:393-399).

2008

"(ME)CFS is characterised by immune dysfunctions including chronic immune activation, inflammation, and altered cytokine profiles. T helper 17 (Th17) cells belong to a recently identified subset of T helper cells, with crucial regulatory function in inflammatory and autoimmune processes. Th17 cells are implicated in allergic inflammation, intestinal diseases, central nervous system inflammation, disorders that may all contribute to the pathophysiology of (ME)CFS*…To investigate the role of Th17 cells, and more specifically of the cytokine IL-17F, in the pathogenesis of (ME)CFS, we studied the association between (ME)CFS and the frequency of the IL17F His161Arg variant…**We found a significantly lower prevalence of the His161Arg variant in the (ME)CFS population compared to the control population****… The His161Arg variant antagonises the pro-inflammatory effects of…IL-17F, and thereby exerts a protective effect against asthma. Similarly, we can make the hypothesis that the development and/or maintenance of (ME)CFS involves an increase in the production of IL-17F, and that the expression of the inactive variant confers protection against the disease* (an expression that is significantly lower in patients with (ME)CFS)*….(Our) results suggest a role of TH17 in the pathogenesis of (ME)CFS…The pro-inflammatory effects of Th-17-secreted cytokines are also consistent with other specific dysfunctions observed in (ME)CFS patients: IL-17 and IL-22 can disrupt the blood-brain barrier; Th17 lymphocytes transmigrate across the blood-brain barrier endothelial cells and promote inflammation of the*

central nervous system (and) blood-brain barrier permeability and CNS inflammation is thought to be a key aspect in the pathogenesis of (ME)CFS" (Metzger K et al. Biochem Biophys Res Commun 2008:376(1):231-233).

2008

*"Myalgic encephalomyelitis/chronic fatigue syndrome is a heterogeneous disease….The central problem in the management of patients with ME/CFS is the lack of biomarkers for patient stratification into subgroups according to distinct immune responses, virus infections and neurological abnormalities….**Our data shows for the first time in ME/CFS a cytokine and chemokine profile, which suggests a Th17 shift in subgroups of our cohort. We conclude that cytokine and chemokine patterns in subgroups of ME/CFS can be used diagnostically, as serum biomarkers to stratify patients for appropriate anti-inflammatory, anti-microbial and anti-viral therapeutics"*** (Serum cytokine and chemokine profiles of individuals with myalgic encephalomyelitis (ME) reveal distinct pathogen associated signatures. Vincent C Lombardi, Kenny DeMeirleir, Judy A Mikovits et al. Cytokine 43 (2008):243-262: doi:10.1016/j.cyto2008.07.077).

2008

At the 6th International Conference on HHV-6 & 7 held in June 2008 at Baltimore, Maryland, Day 4 (23rd June 2008) included a presentation by Professor Nancy Klimas, then at the University of Miami, whose presentation was entitled "Immune markers in viral reactivation". She is reported as having said: "***Remember the immune, the autonomic and the neuroendocrine (systems) are over-lapping….the pathognomonic thing in (ME)CFS is this over-activated immune system…the immune system is antigen-driven.*** *Look for the antigen when you have an activated system….There are only so many things that can activate and drive a system: a pathogen, or more than one pathogen; an allergen; sympathetic nervous system activation of the immune system…and autoimmunity, so* ***– how many different ways might you turn on the button and leave it pushed on – well, maybe five different ways….And that's what the clues are we have here….anything that overdrives a system can turn on the pro-inflammatory cytokine cascade..(that) is turned on in the sickest group of (ME)CFS patients. Apoptosis is when a cell has been on so long it's been driven into cell death. If you push the button on (for) so long and don't release it, the cell will apoptose, and that's been shown in many different cell lines, including T cells and neutrophils. Functional defects that we (and others) have shown (include) natural killer cell dysfunction; cytotoxic T-cell abnormalities; (abnormally low cell content of) perforin and granzyme, and macrophage antibody production abnormalities (very important in sustaining long-term inflammatory responses). We've shown NK cell function to be different in (ME)CFS, and significantly different – we think this is a useful biomarker. It's certainly one that circles an important group in (ME)CFS….****If you split the chronic fatigue patients into fairly normal NK-cell function versus abnormal NK-cell function, you find that the SF-36* (fatigue scale) *is significantly different between these two groups, so again immune dysfunction is correlating with the severity of illness in this patient population. A different objective marker of severity is the PASAT* (cognitive assessment tool) *– how well your higher levels of thinking are working, and again (there is) a low NK and a normal NK split, and the more severely impaired NK-cell function people have more impaired cognitive function".* Looking at lymphocyte activation and at the percentage of CD2+CD26+ lymphocytes, Professor Klimas said: ***"This is probably the only study I know of in (ME)CFS that looked for surrogate cytotoxic T-cell function and..it's not there….we see a significant difference across the board on the amount of CD26 expression on these cells. Now this is an important thing to see. There are more cells expressing this, there's more activation, but on a per cell basis, the ability of these cells to actually put that marker where it is on the receptor – which is a very important functional marker – is quite a bit lower than the controls. So there's more activation, but the functional ability of the cell to express that marker…is diminished, and it's a very significant thing…we think this is a very good biomarker for circling the group that is (ME)CFS…..Neuropeptide Y is a very active substance that has many functions across brain and immune system, so we looked at this, thinking maybe this might be a biomarker (and) sure enough we find neuropeptide Y is elevated as compared to controls in a very significant***

way….the higher it is, the worse the function of the patient….(In summary) (1) The immunologic changes seen in (ME)CFS and GWI are consistent with that seen in chronic viral illnesses (2) Immune dysregulation has been extensively studied, and patterns that would reasonably leave the subject vulnerable to viral reactivation have been shown (3) In considering clinical trials, consideration of immune modulators should be considered, together with antiviral therapies. To sum up, the immune changes that we see in (ME)CFS are absolutely what you should see in a chronic viral state; the cells that clear viruses that are latent that are trying to reactivate – the very cells that prevent reactivation of latent viruses – are the ones that are most dysfunctional. It's an important point to be made….NKCC and intracellular perforin are biomarkers for (ME)CFS. CD2+26+ lymphocytes, rmolCD26 on lymphocytes and sCD26 in plasma are likely to be biomarkers for (ME)CFS. NPT is elevated in (ME)CFS; this may be an important biomarker and has high correlation with cognitive symptoms…. The NK cell is a good surrogate marker for the severity of the illness (and) so is the perforin content, so is the granzyme content (and) it's also important to recognise that the cytotoxic T-cell is equally affected. Finally, these biomarkers coming from immunology-land might be very very useful in clinical trials".

2009

On 20th February 2009 Professor Nancy Klimas gave an interview and an international press release in which she said: "*A biomarker for ME/CFS may be less than two years away….We are closing in on being able to identify the root causes of* ***a disease which affects millions of people around the world – one that is poorly understood and treated by the medical community****….No longer will those afflicted be dismissed by the medical community and, all too often, by their own family and friends as having that 'yuppie thing'….****There are at least three, perhaps even seven, sub-groups of what we call ME/CFS…they may be thought of as three to seven different conditions with closely related symptoms…ME/CFS is a world wide problem that afflicts at least 28 million people, perhaps many more than that****….The disease is so widespread that…a clearly focused international approach will clearly and dramatically speed up…the benefits for those afflicted".* The interviewer commented that this was simply a deeply concerned and compassionate physician and research scientist speaking about that to which she has devoted her life (Co-Cure NOT; RES 24th February 2009).

2009

The world's most knowledgeable ME/CFS scientists and clinicians met at the 9th International Association for ME/CFS Research and Clinical Conference (formerly the American Association for CFS – AACFS – but now the IACFS/ME) held on 12th – 16th March 2009 in Reno, Nevada.

Of special note is that **Professor Leonard Jason, a world-renowned ME/CFS investigator from De Paul University, USA, reported in his presentation "Activity Management" that one group of ME/CFS patients did not benefit from cognitive behavioural interventions: this was the subset of patients whose laboratory investigations showed them to be the most severely affected and who had increased immune dysfunction and low cortisol levels.**

In his Summary of the Reno Conference, Professor Charles Lapp noted that:

- **the metabolic, adrenergic and immune ion channel receptors were up-regulated for days after exercise in people with ME/CFS, with virtually no up-regulation in healthy controls** -- metabolic, adrenergic and immune ion channel receptor mRNA markedly increases in people with ME/CFS but not in healthy controls

- Professor Mary Ann Fletcher (University of Miami) provided evidence that **neuropeptide Y (NPY), a neurotransmitter that is concentrated in sympathetic nerve endings, is elevated in people with ME/CFS in relation to stress much more than in normal controls**

- from presentations by Dr Vincent Lombardi and Professor Nancy Klimas, it was indisputable that numerous cytokines were significantly different in subjects and controls

- **IL-8 and IL-15 were decreased in patients with ME/CFS, while the pro-inflammatory cytokines (TNFβ, IL-1α, IL-1β and IL-6) and Type 2 cytokines (IL-4, IL-5) were increased in ME/CFS, and the anti-inflammatory cytokine IL-13 was reduced: this is consistent with the Th2 or up-regulated immune pattern usually seen in ME/CFS**

- Dr Marc Fremont from Belgium showed that **bowel dysfunction** (dysbiosis, leaky gut, viral infections of the gastric mucosa) **is frequently seen in ME/CFS and there is also a Th1/Th2 immune imbalance. Th1 (normal immunity) is antagonistic to the Th17 immune axis. Th17 cells are crucial regulators of inflammation and autoimmunity, and alterations of the Th17 pathway are frequently associated with intestinal disorders such as irritable bowel syndrome. Th17 cells produce IL-17F protein and a variant known as His161Arg, which confers protection against inflammation. His161Arg was found in only 6% of people with ME/CFS. This suggests that the Th17 axis and intestinal dysfunction are involved in causing inflammation and possibly in the pathogenesis of ME/CFS**

- The conference confirmed that multiple bodily systems are involved in ME/CFS (this is important, as Wessely School psychiatrists insist that the higher the number of bodily symptoms, the greater the certainty of a somatoform disorder)

- Possible biomarkers include: salivary HHV6; ATP profiling of ion channel receptors; mitochdondrial energy score; cytokine and chemokine analysis; near-infrared; EEG profiles; low molecular weight RNase L, and HLA haplotype 4.3.53, MSH, VIP, C4a.

2009

In "Contemporary Challenges in Autoimmunity", the Annals of the New York Academy of Sciences published several articles looking at autoimmunity in (ME)CFS. One such paper states: "***In association with (ME)CFS physiopathology, immune imbalance, abnormal cytokine profile or cytokine genes, and decreased serum concentrations of complement components have been reported…Many studies have shown the presence of several autoantibodies in (ME)CFS patients. Antibodies to diverse cell nuclear components, phospholipids, neuronal components, neurotransmitters, as well as antibodies against some neurotransmitter receptors of the central nervous system have been described***". The authors consider the different types of antibodies that have been reported in (ME)CFS patients and consider in particular antibodies to nuclear components (52% of (ME)CFS patients are reported as having autoantibodies to components of the nuclear envelope, particularly to lamin B1 molecule); to neurotransmitters and receptors (especially to neurotransmitters such as serotonin (5H-T), adrenals, ACTH and to receptors such as muscarinic cholinergic receptor I and μ-opioid receptor 1), and to diverse micro-organisms, noting that serum levels of IgA were significantly correlated to the severity of illness. The authors state that the results showed that enterobacteria might be involved in the aetiology of (ME)CFS and that **an increased gut-intestinal permeability could cause dysregulation of the immune response to the LPS of gram-negative enterobacteria**. The authors note that for many years, enterovirus infection has been associated with (ME)CFS and they note: "***However, several negative studies***, ***combined with the rise of the psychiatric 'biopsychosocial model' of (ME)CFS have led to a diminished interest in this area***" (OD Ortego-Hernandez et al; Ann N Y Acad Sci 2009:1173:600-6009).

(For the avoidance of doubt, in the above paper the authors cite only two "negative studies" associated with enteroviral infection in (ME)CFS: the first by Lindh G et al [Scand J Infect Dis

1996:28:305-307] used the 1994 CDC criteria which do not exclude those with psychiatric disorder, and the second by McArdle A et al [Clin Sci 1996 90:295-300] was co-authored by Professor Richard Edwards, known for his belief that *"many of the symptoms of these patients could be a consequence of their reduced habitual activities"* [Ergonomics 1988:31:11:1519-1527] and for his objection to the publishing by the ME Association of *"substantial amounts of information on the 'disease' "*).

2009

"Examination of anticardiolipin antibodies (ACAs) in the sera of patients clinically diagnosed with (ME)CFS using an enzyme-linked immunoassay procedure ***demonstrated the presence of immunoglobulin M isotypes in 95% of (ME)CFS serum samples tested. The presence of immunoglobulin G and immunoglobulin A isotypes were also detected in a subset of the samples….Testing for antibodies to cardiolipin is routinely performed as one of a panel of tests for autoimmune disorders. In our studies, the presence of ACA at relatively high titres in patients with (ME)CFS suggests the possibility of alterations to the inner membrane of liver mitochondria, thereby exposing cardiolipin in a manner so as to elicit an antibody response….****A survey of the literature reports ACAs as common serological markers in many different types of diseases, including viral diseases such as illnesses resulting from chemical…exposure…HIV and EBV, haematological cancers including CLL* (chronic lymphocytic leukaemia)*…and autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, autoimmune hepatitis and more.* ***This study demonstrates that a large percentage of patients clinically diagnosed with (ME)CFS have elevated levels of the IgM isotype to cardiolipin (955), suggesting that (ME)CFS may be an autoimmune condition (and) classification of (ME)CFS as an autoimmune disorder may serve to increase the availability of treatment options for patients suffering from this disease.*** *Experiments are under way to elucidate why ACAs are produced in individuals afflicted with (ME)CFS. Such studies include investigating the effects of specific chemical agents…on mitochondrial metabolic pathways that are indicative of reduced or blocked energy production that may lead to the fatigued state in (ME)CFS"* (Yoshitsugi Hokama et al. J Clin Lab Anal 2009:23:210-212).

2009

"Recent research has implicated vitamin D deficiency (serum levels of 25-hydroxyvitamin D <50 nmol/L) with a number of chronic conditions, including autoimmune conditions such as multiple sclerosis, lupus and psoriasis, and chronic conditions such as osteoporosis, osteoarthritis, metabolic syndrome, fibromyalgia and (ME)chronic fatigue syndrome….These findings support the use of 1,25-D as a clinical marker in autoimmune conditions" (Blaney GP et al. Ann N Y Acad Sci 2009:1173:384-390).

2009

*"This study aimed to determine the influence of autoantibodies, polymorphisms in the serotonin pathway, and human leukocyte antigen (HLA) class II genes on age at (ME)CFS onset and symptoms…****Our results reveal that in (ME)CFS, like other autoimmune diseases, different genetic features are related to age at (ME)CFS onset and symptoms****"* (OD Ortega-Hernandez et al. Ann N Y Acad Sci 2009:1173:589-599).

2009

"Cancer and (ME)CFS are both characterised by fatigue and severe disability. Besides fatigue, certain aspects of immune dysfunction appear to be present in both illnesses. *In this regard, a literature review of overlapping immune dysfunction in (ME)CFS and cancer is provided. Special emphasis is given to the relationship between immune dysfunctions and fatigue….****It may be clear that fatigue is a major complaint in both diseases….The immunological problems in particular are clearly apparent and quite similar in both diseases"*** (Mira Meeus, Jo Nijs et al. Anticancer Research 2009:29:4717-4726).

2009

*"(ME)CFS studies from our laboratory and others have described cytokine abnormalities….This study screened plasma factors to identify circulating biomarkers associated with (ME)CFS….****The following cytokines were elevated in (ME)CFS***

compared to controls: LTα, IL-1α, IL-1β, IL-4, IL-5, IL-6, and IL-12. The following cytokines were decreased in (ME)CFS: IL-8, IL-13 and IL-15. Cytokine abnormalities are common in (ME)CFS. In this study, 10 of 16 cytokines examined showed good to fair promise as biomarkers. However, the cytokine changes observed are likely to be more indicative of immune activation and inflammation, rather than specific for (ME)CFS….Many of the symptoms are inflammatory in nature….A significant elevation in the relative amounts of 4 of 5 pro-inflammatory cytokines in peripheral blood plasma of patients with (ME)CFS was found when compared with the controls….In cases, lymphotoxin (LT)α was elevated by 257% and IL-6 by 100% over the controls. (The anti-inflammatory cytokine) IL-13 was significantly lower (15%) in (ME)CFS patients….IL-12 was significantly elevated (120%) and IL-15 decreased 15% in cases compared to controls. (The chemokine) IL-8 (CXCL8) was 42% lower in the (ME)CFS patients….In the (ME)CFS cases we found an unusual pattern of the cytokines that define the CD4 T cell….Allergy is common in (ME)CFS cases….The decreased NK cell cytotoxic and lymphoproliferative activities and increased allergic and autoimmune manifestations in (ME)CFS would be compatible with the hypothesis that the immune system of affected individuals is biased towards a T-helper (Th) 2 type, or humoral immunity-orientated cytokine pattern. The elevations in LTα, IL-1α, IL-1β and IL-6 indicate inflammation, likely to be accompanied by autoantibody production, inappropriate fatigue, myalgia and arthralgia, as well as changes in mood and sleep patterns….Cytokine abnormalities appear to be common in (ME)CFS. Several showed promise as potential biomarkers. The changes from the normal condition indicate immune activation and inflammation….The data from this study support a Th2 shift, pro-inflammatory cytokine up-regulation and down-regulation of important mediators of cytotoxic cell function" (Mary Ann Fletcher, Nancy Klimas et al. Journal of Translational Medicine 2009: 12th November:7:96).

2010

The fifth Invest in ME International Conference was held on 24th May 2010 in London. The immunological aspects of ME/CFS were discussed by Professor Nancy Klimas (Miami), who informed attendees that **there is already a biomarker for ME/CFS – NK cell function. This should be considered to be a consistent finding in ME/CFS patients, and it is a good indicator of severity; it is also useful in defining sub-groups. As an NK cell abnormality is not unique to ME/CFS, it cannot be used as a diagnostic biomarker, but NK cell cytotoxicity does appear to be a marker of disease activity in subgroups.** The main theme of her presentation was the need to find biomarkers involved with the immune dysfunction seen in ME/CFS patients. **She summarised important markers of immune activation:**

- **An elevated proportion of CD26 lymphocytes (a specific type of white blood cell) expressing the activation marker dipeptidase IV (DPPIV)**
- **Polarisation of the Th-2 (helper type 2) immune response**
- **Elevation of pro-inflammatory cytokines such as TNFα, interleukin 1 (IL-1) and IL-6 (a cytokine of marked inflammation)**
- **Important defects in immune system function (especially NK cytotoxicity), CD8 and macrophage abnormalities and antibody production.**

Professor Klimas also referred to new research showing that CD26 lymphocyte activation can lead to the production of neuropeptide Y (NPY), which acts on adrenaline responses in the sympathetic nervous system, i.e. on the autonomic control of heart, bladder and bowel function (with acknowledgement to Dr Charles Shepherd).

2010

*"(ME)CFS is a multifactorial disorder that affects various physiological systems including immune and neurological systems….The objective of this present study was to determine deficiencies in lymphocyte function and erythrocyte rheology in (ME)CFS….**Immune dysfunction may therefore be an important contributory factor to the mechanism of (ME)CFS, as indicated by decreases in neutrophil respiratory burst, NK cell activity and NK phenotypes. Thus, immune cell function***

and phenotypes are possible diagnostic biomarkers for (ME)CFS" (Ekua Brenu et al. Journal of Translational Medicine 2010:8:1).

2010

*"(ME)CFS is a complex illness….Instead of searching for a deficiency in any single marker, we propose that (ME)CFS is associated with a profound imbalance in the regulation of immune function. To identify these imbalances we apply network analysis to the co-expression of 16 cytokines in (ME)CFS subjects and healthy controls….**These showed highly attenuated Th1 and Th17 immune responses in (ME)CFS. High Th2 marker expression…pointed to an established Th2 inflammatory milieu*"** (Broderick G, Fuite J, Kreitz A, Vernon SD, Klimas N, Fletcher MA. Brain Behav Immun 2010; 3rd May: Epub ahead of print).

2010

(ME)CFS studies from our laboratory and others described decreased natural killer cell cytotoxicity (NKCC) and elevated proportion of lymphocytes expressing the activation marker DPPIV also known as CD26. However, neither of these assays…are widely accepted for the diagnosis or prognosis of (ME)CFS. ***This study sought to determine if NKCC or DPPIV/CD26 have diagnostic accuracy for (ME)CFS….Cytotoxic function of NK cells for 176 (ME)CFS subjects was significantly lower than in the 230 controls….By ROC*** (receiver operating curve) ***analysis, NKCC and three methods of measuring DPPIC/CD26 examined in this study had potential as biomarkers for (ME)CFS****….Abnormalities in DPPIV/CD26 and in NK cell function have particular relevance to the possible role of infection in the initiation and/or the persistence of (ME)CFS….**The predominance of evidence indicating that people with (ME)CFS have decreased function of NK cells and abnormal activation of T and NK cells was supported by this study….The findings of this study give support to the concept that cause and/or the pathophysiology of (ME)CFS are related to infection…The spectre of infectious disease further emphasises the significance of this research to public health"* (MA Fletcher, Gordon Broderick, Nancy G Klimas et al. PloS ONE 5(5): e10817. doi:10.1371/journal.pone.0010817).

2010

On 16th June 2010 Professor Nancy Klimas was quoted in an interview: "***The low NK cell function group are sicker, have more inflammation, more evidence of viral reactivation….NK cells are important, but they also reflect cytotoxic cell function – and that may be even more important. Having said that, most (ME)CFS patients have poor NK cell function; there is poor and poorer still".*** When asked by the interviewer: "*Is natural killer cell dysfunction in ME/CFS the T-helper cell dysfunction of AIDS and if so, why doesn't it get more attention?*", Professor Klimas replied: "*Well, you have to agree that having so many people die of AIDS was impossible to ignore….**my (ME)CFS patients are much more ill day to day, and yes, some of them die from (ME)CFS related conditions. But the misery quotient in (ME)CFS is terribly high day in and day out*" (http://phoenixrising.me/archives/1606).

2010

*"Participants with (ME)CFS were grouped into viral and non-viral onset fatigue categories and were assessed for differential immunological marker expression….The viral in comparison to the non-viral group demonstrated significant elevations in several Th1 type subsets….The viral group demonstrated a pattern of activation that differed from that of the group with a non-viral aetiology….**These findings imply that the homeostatic mechanism responsible for the regulation of the Th 1 (cell-mediated) and Th2 (humoral) immune responses is disturbed in (ME)CFS….In this sample, the viral group demonstrated elevations in this and the CD4+ and CD2+CD26+ subsets, which suggests an on-going process of systemic inflammation. The present findings support the premise that reductions in the efficacy with which natural killer cells are able to eliminate target cells, concomitant with elevations in activated T-cell subsets, may contribute to the maintenance of inflammation and immune activation"*** (Nicole Porter, Leonard A Jason, Mary Ann Fletcher et al. Journal of Behavioural and Neuroscience Research 2010:8:(2):1-8).

2010

At the CFSAC Science Day meeting on 12th October 2010, Professor Nancy Klimas is reported to have said that **chronic immune activation is a key component of the systems imbalance seen in (ME)CFS; that IgG1 and IgG3 are also skewed; that the more symptomatic patients are, the worse their lymphocytes are functioning; that patients with poor NK cell function have less perforin function in their NK cells; that NK cell function is a very good indicator of the severity of the illness; that neuropeptide Y goes up in (ME)CFS patients and it is an important link to the autonomic nervous system – the higher the neuropeptide Y, the more significantly ill patients are, and that neuropeptide Y has links to the cardio-respiratory system and the immune system as well as to other systems; that pro-inflammatory cytokines are ALL elevated, some more than others, with IL-1 β being the most dramatic; that Type 2 cytokines are elevated and are skewed to allergy and autoimmunity; that IL-6 is a great biomarker in the (ME)CFS population; that there is a blunted adrenal axis and abnormal serotonin function; that cortisol levels are abnormal and the physiological response to stress in (ME)CFS is very poor (*"the connectedness of the endocrine stress response and the immune response is very blunted"*); that in (ME)CFS, 25 genes are expressed differently than in healthy controls, but when exercising, one sees many more genes being differently expressed and that exercising is a very, very impressive tool to understand things, as it is an autonomic trigger and that exercise (autonomic stimulus) is enough to inflame pathways; that other diseases with these markers activated include lymphoproliferative disorders and chronic viruses; that (ME)CFS patients are vitamin D deficient and B12 deficient; that(ME)CFS patients have mitochondrial dysfunction; that "*we have biomarkers*"; that "*you can subgroup by symptom and severity*"; that "*I think I get a pretty good handle on pointing out inflammation with cytokine assays*"; that enteroviruses are very important and that *"herpes, coxsackie, endogenous viruses – all could reactivate*"; that the immune system is a very important player in this disease; that abnormalities seen in the immune system are consistent: immune activation, inflammation, cytokine dysregulation, cellular abnormalities, which are typically seen in infection or autoimmunity (because cytotoxic T-cells are affected, this leans more to infection than to autoimmunity, but autoimmunity is still an important issue)** (http://www.facebook.com/pages/XMRV-Global-Action/216740433250#!/notes/xmrv-global-action/here-is-our-close-transcript-of-the-first-part-of-the-cfsac-science-day/451191706796).

2010

In November 2010 Professor Klimas visited New Zealand on a lecture tour addressing doctors in Auckland, Dunedin and Wellington; the following are from notes taken by a NZ patient with ME, JillNZ, on www.mecfsforums.com. **Professor Klimas likes the Canadian Consensus Criteria in preference to the Fukuda criteria because the CCC emphasise post-exertional malaise, which is unique to (ME)CFS; in the last 20 years her team found chronic immune activation (Th2 shift, DR CD26 expression, TNFα, IL-1, IL-6) and defects (NK cells, CD8 -- cells do not have enough perforin or granzymes) and macrophages are abnormal: *"If you had a chronic virus the immune system would look EXACTLY like this; it doesn't prove it yet, though, because the pattern is also consistent with an autoimmune problem"*; the immune pattern correlates with severity: those with more problems have higher numbers and scores of immune abnormalities; various viruses have been found to be (re)activated – EBV, CMV, HHV6, enteroviruses – all baggage viruses which should remain latent but which have interestingly been found to be activated in (ME)CFS, and something needs to be driving this; we have to remember that blood is not the only reservoir and we need to look at tissue as Chia has shown; a virus does not have to be whole to cause problems; exercise will normally increase cortisol, which acts to control inflammation, but in (ME)CFS, when patients exercise, cortisol goes down and inflammation goes unchecked and gets worse, with pain and delayed autonomic symptoms; the autonomic problems can cause gut motility issues and cerebral perfusion slows down, giving rise to cognitive impairment; her new Dynamic Modelling study looked at 105 patients who used an exercycle for 8 minutes, with blood being drawn at VO2 Max, then again 4 hours later to see all the genes that were turned on and turned off: in (ME)CFS, at VO2 max, it was all the inflammatory cytokines that were turned on (and increased TNFα has 80 downstream effects on**

the body); four hours later, it was the autonomic genes that showed up. The study that she was presenting in Australia reveals 7 or 8 biomarkers for the illness. (ME)CFS patients should not donate organs; a Holter monitor should be used to look at the heart over a few days -- and a good cardiologist is needed because not all will know about cardiac problems in (ME)CFS.

2010

Following her visit to New Zealand, as one of the world's leading immunology researchers, in December 2010 Professor Klimas presented her team's findings at Bond University's Faculty of Health Sciences and Medicine International Science Symposium on ME/CFS held on 3rd-4th December 2010, Gold Coast, Queensland, Australia, as reported by Dr Rosamund Vallings from New Zealand, extracts from whose summary are reproduced with grateful acknowledgement.

Professor Klimas presented a systems biology approach to (ME)CFS. She described (ME)CFS as a disorder of homeostatic imbalance and briefly outlined her 25 year involvement with the disorder, saying she initially worked on the theory that it was a chronic immune activation syndrome, but it was next recognised as a neuro-inflammatory disorder, and now genomics have become involved. Repeating some of her presentation in New Zealand (see above), she described an exercise challenge of 8 minutes with measurement of VO2 max, **and the evidence that the immunological pathways affected were mainly inflammatory, with the immune cascade leading to many symptoms 4 hours later. Those symptoms involved the endocrine, immune, autonomic and neurological systems. The genes regulating NK cell function which included abnormal perforin and granzyme levels were specifically affected. In this study there was persistent inflammation. There was a huge cascade effect after 8 minutes which persisted 4 hours later. This study confirms that graded exercise is not good for those with (ME)CFS,** and patients must stop exercise well short of the aerobic threshold.

Other presentations made included that by Hugh Perry, Professor of Experimental Neuropathology, University of Southampton, who discussed how systems behave during inflammation, for example, "feeling ill", and how infection leads to an inflammatory response with release of cytokines which then communicate with the brain, leading to malaise; he noted that systemic inflammation activates selective brain regions, a mechanism that works through macrophages in the brain via the blood-brain barrier.

Professor Mary Ann Fletcher (University of Miami) presented her work on biomarkers for (ME)CFS, initially looking at NK cell function and the diminution of perforin and granzyme, then at **neuropeptide Y , which is involved in the stress reaction and she showed how, in a controlled study, NPY was considerably higher in (ME)CFS compared with controls and how ROC analysis showed discrimination between (ME)CFS patients and controls, where NPY was found to be 80% sensitive in (ME)CFS. NYP also correlates with disease severity in (ME)CFS.**

Ekua Brenu (PhD candidate, Bond University, Queensland, Australia, under the direction of Professor Sonya Marshall-Gradisnik, one of Australia's foremost researchers in neuroimmunology) had looked at innate and adaptive immunity in (ME)CFS seeking biomarkers in a study of 253 patients and 100 controls at baseline and at 6 months. **Cytotoxic activity of NK cells and CD8+T cells was significantly reduced, and perforin and granzyme activity was reduced. When looking at NK cell phenotypes, CD56 bright cells were significantly diminished. Cytokine secretion from CD+4 T cells showed significant elevation of IL-10, IFNα and TNF; FOXP3 expression was also heightened in the (ME)CFS group. Vaso-active intestinal peptide (VIP, an endoegenous and exogenous immunomodulator) receptors were also investigated and found to be significantly elevated.**

Donald Staines (Bond University, Gold Coast, Australia; Associate Professor and Public Health Physician at PHANU – Australia's Public Health and Neuroimmunology Unit), considered whether autoimmunity affecting vaso-active neuropeptides suggest a pathomechanism for (ME)CFS, as (ME)CFS may be associated with autoimmunity affecting the function of vaso-active neuropeptides such as VIP and PACAP (pituitary adenylate cyclase activating peptide); VIP/PACAP synergism is involved with potentiation of cardiac

firing, anti-apoptosis function, 91amp and insulin control, hypoxia regulation and glutamate metabolism.

2010

"(ME)CFS is a complex, multi-symptom illness with a multi-system pathogenesis involving alterations in the nervous, endocrine and immune systems….Plasma levels of NPY are reported to be elevated in other complex multi-symptom illnesses associated with immunologic dysfunction, including…systemic lupus erythematosus (SLE)…. Given these reports, it seemed likely that plasma NPY would be elevated in (ME)CFS…. ***We tested and confirmed that elevation of peripheral NPY occurs in (ME)CFS and that elevation of NPY is associated with severity of stress, negative mood and clinical symptoms….Immune activation and inflammation are postulated to be principle components in the pathophysiology of (ME)CFS….Normally cortisol induces a down-regulation of inflammation. However, this mechanism is disrupted in the typically hypocortisolic (ME)CFS patient….Dysautonomic conditions…have been reported in (ME)CFS patients….A recent study from our group demonstrated reduced stroke volume and cardiac output in more severely afflicted (ME)CFS patients….Of interest is the finding…that NPY inhibits the production of cortisol in human adrenal H295R cells via the Y1 receptor….This study is the first in the (ME)CFS literature to report that plasma NPY is significantly elevated over healthy controls….*** *Duration of this illness typically exceeds 10 years. Persistence is likely to involve complex interaction of immune, autonomic and neuroendocrine regulation"* (Neuropeptide Y: a biomarker for symptom severity in chronic fatigue syndrome. Mary Ann Fletcher, Gordon Broderick, Nancy Klimas et al. Behavioural and Brain Functions 2010: 6:76 doi:10.1186/1744-9081-6-76).

2011

"Heterologous immunity is a common phenomenon present in all infections. Most of the time it is beneficial…but in some individuals that have the wrong crossreactive response it leads to a cascade of events that result in severe immunopathology*. Infections have been associated with autoimmune diseases such as diabetes, multiple sclerosis and lupus erythematosus, but also with unusual autoimmune-like pathologies where the immune system appears dsyregulated, such as sarcoidosis, colitis…****and (ME)CFS****"* (Selin LK et al. Autoimmunity 2010: Jan 20. Epub ahead of print).

2011

On 29th April 2011 Dr Daniel Peterson gave a presentation at Calgary, Alberta, to medical practitioners. He said that cytokines, low NK cell function, increased activation markers, oxidative stress and mitochondrial dysfunction are a few of the possible markers found in ME/CFS patients, and that while there is no diagnostic test, there are definitive biomarkers for ME. He said that **an association has been found between several critical human molecules such as the thyroid peroxidase protein and leucotropic human herpes viruses, which suggests a mechanism for the commonly reported finding of increased prevalence of autoantibodies in people with ME**. Dr Peterson said he is involved with a large study being conducted at Bond University, Gold Coast, Australia, that is looking at NK cell phenotype and function; **he recommends measuring NK cell function for a diagnosis of ME, as it is the most reliable marker for ME** (reported by Anne-Marie Woynillowicz Kemp: Co-Cure NOT: 12th May 2011).

2011

*"****Derangement of the interaction between the immune and neuroendocrine systems represents one of the major mechanisms in the development of (ME)CFS.*** *Induction of (ME)CFS by i.p. administration of the synthetic double-stranded RNA poly I:C provides a suitable experimental model for studying these mechanisms…****The results lead to the conclusion that impairments between the immune and neuroendocrine systems during the development of (ME)CFS, including changes in the hypothalamo-hypophyseal-adrenocortical system (HHACS) activity, are mediated both at the level of changes in immunocompetent cells and directly on brain cell membranes****"* (Rybakina EG et al; Research Institute of Experimental Medicine, Russian Academy of Medical Sciences. Neurosci Behav Physiol 2011: 41(2):198-205).

2011

"Compared to healthy controls (ME)CFS patients displayed significant increases in IL-10, IFN-gamma, TNF alpha, CD4+CD25+ T cells, FOXP3 and vasoactive intestinal peptide receptor 2 expression. Cytotoxic activity of NK and CD8+ T cells and NK phenotypes, in particular the CD56 bright NK cells were significantly decreased in (ME)CFS patients. Additionally granzyme A and granzyme K expression were reduced….These data suggest significant dysregulation of the immune system in (ME)CFS patients" (Ekua Brenu, Don R Staines, Nancy G Klimas et al. Journal of Translational Medicine 2011: 9:81doi:10.1186/1479-5876-9-81).

2011

*"(ME)CFS is characterised by unexplained fatigue…with a constellation of other symptoms****….Recently, the AISA (autoimmune/inflammatory syndrome induced by adjuvants) syndrome was recognised, indicating the possible contribution of adjuvants and vaccines to the development of autoimmunity"*** (Hemda Rosenblum et al. Infectious Diseases Clinics of North America. Elsevier Inc. doi:10.1016/j.idc.2011.07.012).

2011

The tenth IACFS International Research and Clinical Conference was held on 22nd-25th September 2011 in Ottawa, Canada. It was entitled "Translating Evidence into Practice". The immunology section ("The Latest Research in Immunology"), chaired by Professor Nancy Klimas, included the following:

Ekua Brenu (PhD candidate, Bond University, Queensland, Australia, et al): Cell specific immune investigations have demonstrated a possible link between (ME)CFS and failure to maintain immunological homeostasis. **The most common immune cells with known dysfunction in (ME)CFS are cytotoxic cells, NK cells and CD8+T cells. This study examined cytotoxic function and markers in (ME)CFS patients at 6 month intervals to determine the stability of these observations over time. Preliminary results indicated that compared with healthy controls, (ME)CFS patients demonstrate significant decreases in cytotoxic activity at baseline, at 6 months and at 12 months. Additionally, NK CD56 bright cells remained decreased in (ME)CFS patients. The study demonstrated and confirmed reduced immune function in patients with (ME)CFS and substantiates the use of NK cell cytotoxicity as a biomarker for (ME)CFS.**

Ekua Brenu presented a further study which suggested that **the cytokine profile in (ME)CFS changes during disease progression and that this may be associated with disease severity, hence the need to match laboratory findings with the clinical state of the patient with (ME)CFS.**

Mangalathu S Rajeevan, Elizabeth Unger et al (CDC, Atlanta) said there is evidence that immune and inflammatory alterations are important in (ME)CFS, so they set out to determine if genetic variants in inflammation and immune pathways could be linked to (ME)CFS. **Compared with non-fatigued controls, (ME)CFS was associated with 34 functionally relevant SNPs (single nucleotide polymorphisms). Twelve of these SNPs are genes playing a role in pathways related to complement cascade, chemokines, cytokine/cytokine signalling and Toll-like receptor signalling. The authors concluded that this study identified a number of novel and functionally relevant genetic variants in complement cascade, chemokine and cytokine signalling pathways associated with (ME)CFS.** Of note is the rider stating: "*The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agency"* (i.e. the CDC).

Jeanna M Harvey (MD candidate, University of Miami), together with Professors Mary Ann Fletcher and Nancy Klimas, looked at twelve biomarkers that had significant changes as a result of exercise in three groups (Gulf War Syndrome, ME/CFS and healthy controls). **Upon exercise, the number of CD26+ lymphocytes was higher for GWS and the healthy controls but lower in patients with (ME)CFS. The authors concluded that biomarker measurement during the course of an aerobic exercise challenge indicates major differences among GWS, (ME)CFS and healthy controls which may help the understanding of these complex disorders.**

Maria A Vera (University of Miami), together with Professors Mary Ann Fletcher and Nancy Klimas, noted that Metabolic Syndrome (MetSd) is a known risk factor for cardiovascular and cerebrovascular disease, and that previous studies have shown that patients with (ME)CFS were twice as likely to have metabolic syndrome as controls. They set out to compare cytokine levels in patients with (ME)CFS with and without metabolic syndrome. **They concluded that the prevalence of metabolic syndrome in an (ME)CFS population was 26%, and that similarly to their previously reported findings in (ME)CFS, patients with both (ME)CFS and metabolic syndrome had abnormalities in pro-inflammatory, Th2, Th1 and IL-8 compared with healthy controls and were biased towards a Th2 cytokine pattern, accompanied by autoantibody production.** The investigators recommend that large longitudinal studies should be performed to determine the contributing factors to this increased risk.

Professors Mary Ann Fletcher and Nancy Klimas (Miami) looked for biomarkers in (ME)CFS. **Prospective biomarkers included NK cell cytotoxicity (NKCC), T lymphocyte proliferation in vitro in response to mitogen (LPA), lymphocyte activation markers (CD26, CD38), 16 plasma cytokines and neuropeptide Y. The results provided credible biomarker status for NKCC, LPA, and markers of lymphocyte activation in (ME)CFS. A significant elevation in the relative amounts of four of five pro-inflammatory cytokines in peripheral blood plasma of patients with (ME)CFS was found when compared with the controls. Both IL-4 and IL-5 were elevated in (ME)CFS. The anti-inflammatory cytokine IL-3 was significantly lower (15% lower) in (ME)CFS patients. IL-12 was significantly elevated (120% higher) and IL-15 decreased 15% in cases compared with controls. IL-8 was 42% lower in the (ME)CFS patients. The stress hormone NPY was elevated in plasma of (ME)CFS patients and positively correlated with perceived stress. The authors concluded that fifteen useful biomarkers were identified in their studies, and that the differences in these markers compared with controls give important information regarding the pathophysiology of (ME)CFS. The association of low LPA response, elevated proportion of activated CD4 and CD8 T cells, defective NKCC, elevated Th2 cytokines in (ME)CFS cases suggests that T cells are metabolically limited in performing their helper function. All but one of the inflammatory cytokines were elevated, as was the stress hormone NPY, supporting the hypotheses that inflammation and abnormal stress responses are important components in the pathophysiology of (ME)CFS.**

Ekua Brenu et al (Bond University, Queensland) studied the effects of vaccination on immune function in (ME)CFS. Noting patients' inability to tolerate certain toxins and their hypersensitivity, they set out to examine the effects of routine vaccination on immune function in patients with (ME)CFS. **They concluded that their findings suggest a potential role of vaccines in the pathophysiology of (ME)CFS.**
It is notable that Dr Daniel Peterson is on record in relation to the above study at Bond University saying on 14th October 2011 that the investigators assessed immune functioning before and after people with (ME)CFS were vaccinated and they found evidence that vaccinations may be significantly affecting immune functioning (http://forums.phoenixrising.me/content.php?490-Dr-Peterson-Talks-On-Diagnosing-Treatin-XMRV-CFS-MECFS-chronic-fatigue-syndrome).

This may tie in with the AISA syndrome (autoimmune/inflammatory syndrome induced by adjuvants in vaccines) noted by Rosenblum et al in Infectious Diseases of North America mentioned above.

It is further notable that on 23rd March 2012 neurosurgeon Dr Russell Blaylock was reported as saying in an interview that vaccines switch the immune system to Th2 and that they suppress immunity rather than boosting it by confusing the immune system and altering the way it responds to viruses and bacteria: "*We found that, in fact, (vaccination) causes the immune system to switch to what we call Th2-type cytokine production which inhibits immunity. And your major protection against viruses…is your cellular immunity. Well, vaccines don't stimulate cellular immunity at all, in fact they suppress it*" (http://tv.naturalnews.com/v.asp?v=DFBE7C32CBDBF43B7342333B7D827EB0).

2011

"There is evidence that inflammatory pathways and cell-mediated immunity (CMI) play an

important role in the pathophysiology of ME/CFS. *In this study we therefore measured plasma IL-1, TNFα, and PMN-elastase, and serum neopterin and lysozyme in 107 patients with ME/CFS, 37 patients with chronic fatigue (CF) and 20 normal controls. Serum IL-1, TNFα, neopterin and lysozyme are significantly higher in patients with ME/CFS than in controls and CF patients.* ***Plasma PMN-elastase is significantly higher in patients with ME/CFS than in controls and CF patients*** *and higher in the latter than in controls….****The results suggest that characteristic symptoms of ME/CFS, such as fatigue, autonomic symptoms and a flu-like malaise, may be caused by inflammatory mediators****"* (Maes M, Twisk FN, Kubera M, Ringel K. J Affect Disord 2011: Oct 3 Epub ahead of print).

2011

In a presentation given on 22nd October 2011 in Seville, Spain, Kenny DeMeirleir (Professor of Physiology, Pathophysiology and Medicine, Vrije Universiteit, Brussels) provided a list of laboratory tests that support the clinical diagnosis of ME/CFS; those involving the immune system included the following:

Immunophenotype:

- Total number of lymphocytes
- CD4/CD8 ratio
- CD4+ lymphocytes
- CD8+ lymphocytes
- Ratio of NK cells
- B cells
- Soluble CD14 (increased in 90% of ME/CFS patients and correlates with severity)
- CD57 lymphocytes (low in most ME/CFS patients)
- Leucocyte elastase activity (increased in a sub-group of patients)
- C4a (increased in 80% of patients)
- Expression of perforin mRNA
- IgM and IgG

Cytokines: (cytokine serum levels)

- IL-8, MCP1, MIP-1β
- IL-6, IL-10
- IL-12
- TGFβ 1
- TNFα

Food intolerance panel of IgG:

- Casein
- Gluten
- Lactose
- Tissue transglutaminase and gliadin antibodies (IgA / IgG)
- Defective lactase gene.

It will be recalled that, due to the influence of the Wessely School, none of these tests is permitted in the UK National Health Service for people thought to have ME/CFS.

2011

In October 2011 the International Consensus Criteria for Myalgic Encephalomyelitis were published in the Journal of Internal Medicine 2011:270:4:327-338

(http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/abstract).

The following is an extract on "Immune Impairment", together with the references cited:

"*Publications describe decreased natural killer cell signalling and function, abnormal growth factor profiles, decreased neutrophil respiratory bursts and Th1, with a shift towards a Th2 profile [4–8, 92, 93]. Chronic immune activation [27], increases in inflammatory cytokines, pro-inflammatory alleles [4–8, 94–96], chemokines and T lymphocytes and dysregulation of the antiviral ribonuclease L (RNaseL) pathway [62, 97–100] may play a role in causing flu-like symptoms, which aberrantly flare in response to exertion [5,92].*

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2011

"(ME)CFS is a disease of unknown aetiology. Major (ME)CFS symptom relief during cancer chemotherapy in a patient with synchronous (ME)CFS and lymphoma spurred a pilot study of B-lymphocyte depletion using the anti-CD20 antibody Rituximab, which demonstrated significant clinical response.
The…response…suggests that (ME)CFS is an autoimmune disease….The results support the assumption that (ME)CFS is not primarily a mental health disease….The B cells have multiple immune functions, the main ones being antibody production, antigen presentation and regulation of the function and activity of other immune cells, i.e. T-regulatory cells, NK cells and macrophages….We believe the results are best compatible with an autoimmune disease mechanism and that the presented findings may have a major impact on the direction of biomedical research in (ME)CFS" (Oystein Fluge, Olav Mella et al. PloS one: October 2011:6:10:e26358: doi:10.1371/journal.pone.0026358).

Replying on 31st October 2011 to criticisms levelled by van der Meer et al, Dr Fluge pointed out that ***"an autoimmune component is probable in many patients (with ME/CFS)…***(and that) ***(ME)CFS according to Fukuda or Canadian criteria is in many patients a very serious and debilitating disease".***

Commenting on the Norwegian study, Dr Gordon Broderick (Associate Professor, University of Alberta) said: "*As mentioned by the authors, Rituximab is a B-cell suppressor used in the*

treatment of non-Hodgkin's lymphoma. ***Abnormal B-cell activity has long been suspected as playing a key role in (ME)CFS.*** *As early as 2006 Maes and colleagues…presented evidence of increased IgM antibodies directed specifically at cellular products of oxidative and nitrosative stress. That same year, our work with Dr Suzanne Vernon and her colleagues also produced evidence of sustained oxidative stress in circulating immune cells based on their gene expression….****Evidence of altered status in the B-lymphocytes of (ME)CFS patients was found in a study of gene expression conducted by our group…Further work…conducted with Drs Nancy Klimas and Mary Ann Fletcher of the University of Miami documented immune signalling patterns suggestive of an over-active Th2 or B-cell mediated immune response****….In a nutshell, these positive clinical trial results are not only welcome but they represent a logical continuation of a line of investigation that has been ongoing"* (http://www.research1st.com/2011/10/21/broderick).

Also commenting on the Norwegian study, Professor Nancy Klimas said: ***"The recent study of Drs Oystein Fluge and Olav Mella demonstrating significant improvement in ME/CFS patients treated with the B-cell depleting agent Rituximab is a key study for our field. By showing that depleting B cells can cause dramatic improvement, the investigators point the field in the direction of autoimmunity, and autoimmunity caused by an autoantibody. However, there is one other plausible explanation: that the B cells were acting as a reservoir of infection and by depleting the B cell line the viral load can be brought down to the point of suppression by the immune system….I believe that both of these theories deserve vigorous scientific pursuit….Many clinicians fail to realise the severity of the illness that has been termed ME/CFS. This is a profoundly ill population"*** (http://bergento.no/the-mecfs-study-by-mella-and-**fluge-is-a-key-study-for-our-field/** **).**

Conclusion

There can be no possible doubt that ME/CFS is essentially a disorder of the immune system.

Given the extent of the evidence-base (of which the above illustrations may barely scratch the surface), it is incomprehensible how the Wessely School psychiatrists continue to wield such powerful influence over the ME/CFS arena.

Many people deem this situation to be a scandal of epic proportions.

As Dr Vance Spence, a respected medical scientist specialising in vascular medicine in ME/CFS, said in an article on 25th May 2004 in the Derry Journal ("The ME Scandal"): "***I can think of no other illness where such a powerful schism exists between those who suffer from it and those whose responsibility is to care for them. How can it be that an illness that affects between 100,000 and 200,000 persons of all ages in the UK and maybe as many as one million in the United States of America is no longer referred to in medical textbooks, is not cited in medical research indexing systems and rarely features in the syllabus of undergraduate medical education in medical schools? Why have the experiences of these patients been largely ignored, their testimonies…undervalued, even ridiculed, and their requests for assistance met often with prejudice and disbelief?*** (Co-Cure RES, ACT 8th June 2004).

Could the answer lie in just three words: The Wessely School?

On 1st August 2004 John Herd re-published an article he had written seven years earlier (in 1997), saying how profoundly rhetoric has permeated the (ME)CFS arena, and that the tragedy of lasting misperceptions means that it is not enough for doctors to conduct their research and see patients in their clinics – they must speak up about their evidence that ME/CFS is not a psychiatric disorder: "***Throwing forth theories of psychiatric causations of ME/CFS…is not science. Science, hard science, is objective….The proof that transforms theory into science is concrete evidence found in cells…Psychiatric research is…highly interpretive…(it) lacks the concrete evidence of biologic research (and thus) can be driven by its original theories instead of…concrete evidence…"Science" seems to mean different things to different people. Speculation, especially if it comes from a well-known name, in some people's eye becomes fact as soon as it appears in a peer***

reviewed medical journal….Why is anyone listening to self-proclaimed experts who have direct connections with corporate entities that only wish to protect their financial assets?" (Co-Cure ACT, 1st August 2004).

Herd followed this up by saying: "***More and more doctors have become entrenched in an 'all in the head' bias about ME/CFS that is not founded upon evidentiary science. Instead of welcoming advancements of science, their minds have become ever more closed to objective laboratory findings that conflict with their belief systems….Doctors who are uninformed about the illness and those firmly entrenched in flawed ideologic bias may not even bother to read new research articles (so) many patients see no improvement in accessibility to adequate clinical care…Proponents of the idea that ME/CFS is a psychosocial phenomenon have been getting more and more of their articles in the medical journals. They hold a powerful and influential position in the World Health Organisation and in many influential governmental/medical committees….We must find ways to remove ideology and speculation from the equation (and) develop new means of having science speak for itself to break the logjam of flawed ideologic bias"*** (Co-Cure ACT: 19th October 2004).

It is high time for the Wessely School and all to whom they act as advisors to engage with the immunological basis of ME/CFS. As one sufferer pointed out in 2005, attributions do not maintain this illness, any more than they maintain cancer, diabetes, multiple sclerosis, or any other physical illness (Co-Cure ACT: 27th July 2005). In fact, the objective and reproducible evidence plainly shows that ME/CFS is maintained by a dangerously dysregulated immune system.

There is such a gross mismatch between the severity and complexity of ME/CFS and the medical/public perception of the disorder as promulgated by the Wessely School that, until these psychiatrists are held to account (and health care professionals and public alike are informed and educated about the nature of ME/CFS), patients will continue to suffer iatrogenic harm.

Wessely has often claimed that he does not want to get into the fruitless "organic" versus "functional" debate, but many people believe (justifiably, when one reads what he has actually published about people with ME/CFS over the last 25 years) that he has done more than anyone else to fan this particular flame by distorting the perception of the disease; they also believe that he has done much to prevent ME/CFS attaining disease legitimacy and thus to halt not only the progress of medical science but also the provision of care for very sick patients.

The body of biomedical evidence about ME/CFS from across the disciplines is now so extensive that the question repeatedly asked is: at what point will that body of scientific knowledge be so great that it will be considered serious professional misconduct to ignore it and to continue to deceive physicians and patients alike by pretending that it does not exist?

There is a body of informed opinion (including clinicians, medical scientists, lawyers, research analysts, university lecturers and members of other professions) that the General Medical Council ought to be required to assess the Wessely School's fitness to practice medicine: many people are of the view that the Wessely School are a risk to ME/CFS sufferers by their erroneous assertion that ME/CFS patients' multiple symptoms "***have no anatomical or physiological basis***" (Brit J Hosp Med 1994:51:8:421-427), a categoric Wessely School view that has not changed over the intervening 18 years and which seems to be reflected in NICE's proscription of appropriate laboratory tests (in particular, no immunological tests may be carried out); by their ignoring of the biomedical evidence, and by their insistence that ME/CFS is a functional/behavioural disorder and a "***pseudo-disease***" that must not be investigated as this would reinforce sufferers' alleged misperceptions that they are physically sick.

However, even though the national implementation of the Wessely School's personal philosophy is not based on medical science, nothing might come of a complaint to the GMC because, as Dame Janet Smith (The Rt Hon Lady Justice Smith, a High Court Judge and former President of the Council of The Inns of Court) aptly said on 3rd October 2011, the GMC is "***a deeply dysfunctional institution***" (Channel 4; Dispatches).

On 26th March 2012 the Prime Minister, David Cameron, said on television that the dementia situation in the UK is "***a national crisis***".

He needs to be aware that there is also a national crisis with the ME/CFS situation in the UK, where sick people are denied the scientific reality of their disease and instead are coerced into inappropriate psychological interventions that have been shown to make 82% of ME/CFS sufferers worse (http://www.investinme.org/Article400%20Magical%20Medicine.htm).

ME FACTS

Over 20 renowned international experts on ME have provided written statements of concern effectively stating that cognitive behavioural therapy and graded exercise therapy used to support the alleged existence of the "biopsychosocial model" do not work for people with ME (Magical Medicine pp 88-92). Furthermore, numerous trials have shown that not only is the "biopsychosocial model" unsuccessful in the management of ME/CFS but that the model itself is not evidence-based and it may be actively harmful:

-the evidence that behavioural modification techniques have no role in the management of ME/CFS is already significant and has been confirmed by a study in Spain, which found that in ME/CFS patients, the two interventions used to justify the biopsychosocial model (CBT and GET) did not improve HRQL (health-related quality of life) scores at 12 months post-intervention and in fact resulted in worse physical function and bodily pain scores in the intervention group (Nunez M et al;
Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomised controlled trial with 1 year follow-up. Clin Rheumatol 2011, Jan 15: Epub ahead of print)

More Concerns About the Current UK Welfare Reform
http://www.investinme.org/Article-441%20UK%20Welfare%20Reforms.htm

ME STORY

I live in constant fear of a crisis driving me into hospital; our hospitals have shown such lack of consideration for the special needs of patients like me that time spent in hospital is torture (eased only by the incredible kindness shown by some nurses and doctors) and invariably causes further deterioration.

Many days I feel utter despair.
But, unlike some sufferers, over the long years in which I've had severe ME (the illness began mildly and has taken a progressive course) I have at least had periods of respite from the absolute worst of it.

During those periods I was still very ill, but it was possible to enjoy something of life. So in these dark days I know there is a real chance of better times ahead and that keeps me going.

My entire future, and the greatly improved health I so long for, however, currently hinges on luck alone.

This is wrong.

As I lie here, wishing and hoping and simply trying to survive, I (and the thousands like me – severe ME is not rare) should at least have the comfort of knowing that there are many, many well-funded scientists and doctors who are pulling out all the stops in the quest to find a treatment which may restore my health and that the NHS is doing all possible to care for me as I need to be cared for – but I don't.
This wretched, ugly disease is made all the more so through the scandalous lack of research into its most severe form and the lack of necessary, appropriate support for those suffering from it.

This is something that must change.

\- Emily Collingridge

Emily Collingridge passed away in March - losing her fight against this awful disease myalgic encephalomyelitis.
These words were written over many weeks – while Emily still had the strength in her body to do so.

http://www.investinme.org/EmilyCollingridge.htm

PRESENTERS at the 7th INVEST in ME INTERNATIONAL ME/CFS CONFERENCE

Dr Ian Gibson

Dr Ian Gibson, former Labour MP for Norwich North, worked at UEA for 32 years, became dean of the school of biological sciences in 1991 and was head of a cancer research team and set up the Francesca Gunn Leukaemia Laboratory at UEA. In 2011 Dr Gibson received an honorary doctorate of civil law from UEA.
Dr Gibson will chair the conference this year.

Professor Don R Staines

New Directions for ME/CFS Research

Don Staines is a public health physician at Gold Coast Population Health Unit. He has worked in health services management and public health practice in Australia and overseas. His interests include collaborative health initiatives with other countries as well as cross-disciplinary initiatives within health. Communicable diseases as well as post infectious fatigue syndromes are his main research interests. A keen supporter of the Griffith University Medical School, he enjoys teaching and other opportunities to promote awareness of public health in the medical curriculum.

Abstract

Autoimmunity as a plausible hypothesis in the aetiology of ME/CFS has been explored by our research group in Australia since 2004. Recent clinical data from Norway support an autoimmunity hypothesis with benefit from anti-CD20 monoclonal antibody demonstrated in a clinical trial. Autoimmunity remains a challenging area for research with complex interactions between innate and acquired immune system responses. Identification of a putative target for autoimmune attack in ME/CFS remains elusive. Hence a Clinical Autoimmunity Working Group (CAWG) was established to bring autoimmunity and neuroscience specialists together to consider recent clinical data and consider future directions in this research area. Topics discussed included autoimmunity pathomechanisms and presentations, identification of autoimmune targets, laboratory models including experimental autoimmune encephalomyelitis (EAE), vascular changes in the central nervous system, advances in vasoactive neuropeptide (VN) research and novel biomarkers assisting the diagnosis of ME/CFS. Recent developments in purinergic signalling and neurological models of autoimmunity including reactive gliosis, and pathomechanisms involving VNs may contribute to the understanding of CFS/ME. ATP, NO and VIP are now recognised as co-transmitters and may be involved in these pathomechanisms. Moreover gliosis is invariably associated with brain insult and may be a feature of 'virtual' oxygen glucose deprivation likely to occur from VN failure. The neurovascular unit (NVU) has a vital role in cerebral vasculature and immune competency and these functions might be lost in VN compromise. Effects would be expected to be more severe in the CNS where blood brain barrier (BBB) and blood spinal barrier (BSB) function could be compromised by the activation of purinergic receptors and initiation of inflammatory mechanisms. Other organs systems including heart, gut and lung may also be compromised through these pathomechanisms which may in part explain the prolonged and difficult course of CFS/ME. New techniques for investigating BBB and BSB function are being developed and may have applications in this condition. Therapeutic opportunities may arise through renewed understanding of immunological and neuroinflammatory mechanisms involved in ME/CFS.

Dr Sonya Marshall-Gradisnik

Title: Immunological dysfunction as possible biomarkers for Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS)

Dr. Sonya Marshall-Gradisnik is an Associate Professor in Immunology. Since obtaining her PhD (2004) she has received over $4 million dollars in competitive external grant funding. In 2010, Dr Marshall-Gradisnik was awarded the prestigious Queensland Women in Technology Research Award-Rising Star Award for her research into immunological biomarkers for ME/CFS. Dr Marshall-Gradisnik has edited two books, published 52 publications in high impact journals, eight book chapters, and published sixty-four conference abstracts in immunology. She is a reviewer for the Australian Research Council (ARC) and was in 2011 one of the authors of the ME: International Consensus Criteria. Dr Marshall-Gradisnik has recently received the following awards/grants: Queensland Government ($533,000); Queensland Government Co-Investment Fund ($830,000); Mason Foundation ($831, 000) and the Alison Hunter Memorial Foundation Research Grants. Dr Marshall-Gradisnik leads a large research team that is not only developing early diagnosis of immunological biomarkers for ME/CFS but also focusing on gene expression studies in severe and moderate ME/CFS patients. She has received the National Award as Best Young Science Investigator at the Australian Conference for Science and Medicine for her studies into natural killer cell function and genotyping.

Abstract

Sonya Marshall-Gradisnik [2,3,4] Donald R Staines,[1,2] Kevin J Ashton [3] Daniel Peterson [6], Sharni Hardcastle[1,2], Mieke van Driel [2,3,5] and Ekua, Weba Brenu [2,3]

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6. Siera Internal Medicine at Incline Village

Chronic Fatigue Syndrome (CFS) is a multi-factorial disease that may involve disparities in neuro-endocorine immune function. Presently, a number of neuropeptides have been associated with CFS. This may be attributed to their role in regulating immune function. Our research has investigated patients diagnosed with CFS to identify immunological/neuroimmunological and genetic differences in patients compared with non-fatigued controls where our investigations have shown dysfunction in Natural Killer cell lysis, Natural Killer Cell Phenotype, Cytotoxic T cell Cytotoxic Lysis, GZMA lytic protein decreases for NK and T Cytotoxic cell function, Neuropeptide receptor dysfunction (VPAC1R and VPAC2R), Foxp3 expression, Cytokine dysregulation (T-Helper 1 and T-Helper 2 Dysregulation) and microRNA immune regulation in CFS patients compared to non-fatigued controls. These collective studies suggest their application as potential biomarkers for early identification of ME/CFS patients for clinicians.

Professor Hugh Perry

Neuroinflammation in chronic disease

Professor Perry and his team study Inflammation in the CNS and its contribution to Neurological Disease.

The results of this research may help in the development of therapies to treat acute and chronic neurodegenerative conditions, which at present are largely untreated.

Inflammation biology in the brain is a complex subject and requires expertise in many different areas.

The CNS Inflammation Group has collaborations with academic laboratories across the University of Southampton, the UK, as well as with laboratories across Europe.

Abstract

The resident immune cells of the brain, the microglia, are observed to be morphologically activated, express a greater diversity of immune-function related molecules and increase in number during the progression of many chronic

neurodegenerative diseases. Observational studies in human post-mortem material and studies in animal models seek to define the contribution that this innate immune response makes to the pathogenesis and rate of progression of these diseases. It is well recognized that age is a significant risk factor for diseases such as Alzheimer's disease and Parkinson's diseases and that elderly people commonly have systemic comorbidities that give rise to systemic inflammation. There is a growing body of evidence to show that systemic infection and inflammation impact on the progression of chronic neurodegeneration in animal models: this involves the switching of the microglia phenotype from a relatively benign phenotype to an aggressive tissue damaging phenotype by the systemic inflammation. Clinical studies in patients with Alzheimer's disease show that chronic systemic inflammation and acute infections are associated with accelerated cognitive decline and exacerbation of the symptoms of sickness. These observations show that immune to brain communication normally part of our mechanisms for fighting infection may become maladaptive in those with degenerative diseases of the brain. These findings offer new routes to therapeutic interventions to improve the quality of life of those suffering from chronic neurodegenerative disease.

Professor Maria Fitzgerald

An Overview of Chonic Pain Mechanisms

Professor of Developmental Neurobiology Dept Anatomy & Developmental Biology, University College London.

Maria Fitzgerald graduated in Physiological Sciences at Oxford University and studied for a PhD in Physiology at UCL. She was awarded a postdoctoral MRC training fellowship to work with Professor Patrick Wall in the Cerebral Functions Group at UCL and remained in that group as a postdoctoral fellow until starting her own research group in the Anatomy & Developmental Biology Dept at UCL.
She became a Professor of Developmental Neurobiology in 1995 and was elected as a Fellow of the Academy of Medical Sciences in 2000. Maria is Scientific Director of the Paediatric Pain Research Centre at UCL www.pprg.ucl.ac.uk, and is a member of a number of research boards including the Medical Research Council Neurosciences and Mental Health Board, the Scientific Board of the Migraine Trust and the French National Research Agency (ANR).
She is an Editorial Board member of 'Pain' and of 'Pain Research and Clinical Management. Maria has published over 130 research papers and reviews in the area of pain neurobiology (*taken from UCL site* http://www.ucl.ac.uk/npp/research/mfi).

Abstract:

Chronic pain arises from plastic changes in the peripheral and central nervous system. These changes are triggered and may be maintained by an insult to tissues, organs or to the nervous system itself. Damage to the nervous system itself can result in neuropathic pain, a particularly unpleasant chronic pain which is especially difficult to treat. Because neural connections within the sensory and nociceptive systems have been altered, pain can take on a 'life of its own' and no longer require the presence of tissue damage. As a result, the pain will often persist beyond the resolution of the original injury. Thus chronic pain has a clear biological origin, but that origin lies within the nervous system itself and if we are to prevent or treat it effectively we need to understand these neural changes. Poor pain recovery following the resolution of a physical insult can lead to the conclusion that patients are catastrophizing or have aberrant health beliefs, while in fact defined neurobiological changes in neural pain pathways are the source of the problem. This lecture will provide an overview of our current understanding of chronic pain mechanisms.

Dr Mario Delgado

Neuropeptides and their role in chronic disease

Mario Delgado
Institute of Parasitology and Biomedicine, CSIC, Granada, Spain

As a neuroimmunologist, his main research focus has been to understand the bidirectional communication that exists between immune

and neuroendocrine systems. A primary objective of the Delgado laboratory is to identify endogenous anti-inflammatory factors, mainly neuropeptides and hormones, that are produced under inflammatory and autoimmune conditions, with the aim of identifying therapeutic agents for immune disorders where tolerance is compromised.

Abstract:

Vasoactive intestinal peptide (VIP), a 28 aminoacid neuropeptide, is widely distributed in both the central and peripheral nervous system. VIP is released by both neurons and immune cells. Various cell types, including immune cells, express VIP receptors, which act via stimulation of cAMP/protein kinase A pathway. VIP has potent effects as a neurotransmitter, vasodilator and secretagogue, but in the last two decades, numerous works indicate that VIP is a pleiotropic immunomodulatory factor with potential for its therapeutic use in inflammatory, autoimmune and neurodegenerative disorders. Based in our knowledge on VIP, my group have recently characterized other neuroprotective and immunomodulatory neuropeptides, which have been proven to be effective in the treatment of chronic neuroinflammatory and autoimmune diseases. In this meeting, I will highlight the most recent data relevant in the field and we will offer our opinion on how therapy with VIP and other neuropeptides might impact clinical immune diseases, including myalgic encephalomyelitis/chronic fatigue syndrome, and the challenges in this field that must be overcome before achieving medical progress. Finally, we will discuss how a physiologically functional neuropeptide system contributes to general health and how neuropeptides educate our immune system to be tolerant.

Professor James Baraniuk

Systems Biology of Interoceptive Disorders

James N. Baraniuk was born in Alberta, Canada. He earned his honours degree in chemistry and microbiology, medical degree, and unique bachelor's degree in medicine (cardiology) at the University of Manitoba, Winnipeg, Canada. Thereafter, he moved to Akron, OH, USA, for his internship and internal medicine residency at St Thomas Hospital.

After another year of internal medicine residency at Duke University Medical Center, Durham, NC, he trained with Dr C.E. Buckley, III, in allergy and clinical immunology. He moved to the laboratory of Dr Michael Kaliner at the National Institute of Allergy and Infectious Diseases, Bethesda, MD, and there began his long-standing collaboration with Dr Kimihiro Ohkubo. After 2 years studying neuropeptides, he joined Dr Peter Barnes' laboratory at the National Heart and Lung Institute, Brompton Hospital, London, UK. Dr Baraniuk returned to Washington, DC, and Georgetown University, where he is currently Associate Professor with Tenure in the Department of Medicine.

Abstract:

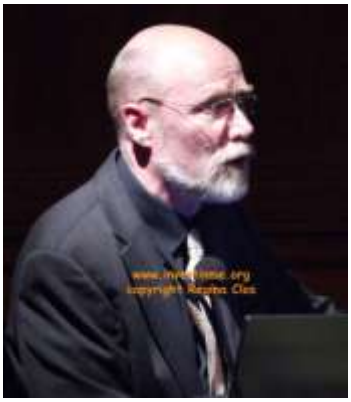
We apply the term interoceptive disorders to encompass symptom complexes with excessive, prolonged perceptions of discomfort stemming from expansion and contraction of the walls of hollow organs [Adam]. Nasal, pharyngeal, bronchial, esophageal, stomach, large and small bowel, bladder, urethra and vagina have extensive networks of sensory neurons in their walls. Mechanical receptors detect the degree of stretching of these nerves and the organ. The molecular mechanisms and proteins of these sensors are still being determined. These will be targets for new classes of drugs to treat nonallergic rhinitis, dyspnea, "nutcracker esophagus", dyspepsia, irritable bowel syndrome, irritable bladder syndrome and vulvodynia. These interoceptive disorders are fundamental to the pathology of ME/CFS and allied disorders as can be demonstrated by analysis of syndrome subtypes using the 1994 Fukuda criteria and questionnaire-based definitions of "fatigue". These criteria suggest that central sensitization of nociceptive sensory input to the spinal cord and brain leads to the pain, tenderness, hyperalgesia and allodynia. Critical mechanisms include (i) increased activation and up regulation of sensor protein systems on peripheral nociceptive nerve endings (peripheral sensitization); (ii) increased glutamate release from peripheral nerves in the dorsal spinal cord; (iii) changes in glutamate and AMPA receptor expression on the secondary,

nociceptive, somatosensory interneurons that convey the pain messages to the thalamus and higher centers; (iv) microglial cell activation that potentiates these effects; (v) modification of inhibitory dorsal horn regulatory interneuron signals with the loss of protective, antinociceptive effects; (vi) development of new synaptic connections by light touch, proprioceptive, and other myelinated neurons onto the nociceptive secondary interneurons so that normally innocent sensations now stimulate pain (allodynia). We propose that similar mechanisms account for increased perception of interoceptive messages to the brain.

Dr. Øystein Fluge and Professor Olav Mella

Institute of Medicine, Section of Oncology, University of Bergen, Norway

Dr. Øystein Fluge received medical degree in 1988 at the University of Bergen, and is a specialist in oncology since 2004. He has worked as a Research Fellow with support from the Norwegian Cancer Society and is now chief physician at the Cancer Department, Haukeland University Hospital. Doctoral work emanates from the Surgical Institute and Department of Molecular Biology, University of Bergen.



Professor Olav Mella and researcher Dr Oystein Fluge from University of Bergen, Haukeland University Hospital, department of oncology are currently conducting a clinical trial on B-lymphocyte Depletion Using the Monoclonal Anti-CD20 Antibody Rituximab in Severely Affected Chronic Fatigue Syndrome Patients. This study is based on pilot patient observations, and experience from the prior study KTS-1-2008. The investigators anticipate that severely affected chronic fatigue syndrome patients may benefit from B-cell depletion therapy using Rituximab induction with maintenance treatment.
The hypothesis is that at least a subset of chronic fatigue syndrome (CFS) patients have an activated immune system involving B-lymphocytes, and that prolonged B-cell depletion may alleviate symptoms.

Professor Indre Bileviciute Ljungar

One year experience of a standardised team-based assessment of suspected ME/CFS in a New ME/CFS-project

Dr. Indre Bileviciute-Ljungar is an associate professor in rehabilitation medicine at Karolinska Institutet and working as a specialist in rehabilitation medicine at ME/CFS-project at Dept. of Rehabilitation Medicine, Karolinska Institutet, Danderyd University Hospital, Stockholm, Sweden. The aim of the team-based ME/CFS-project is to improve the diagnosis of ME/CFS patients, to transfer clinical knowledge to the primary care structures, to establish rehabilitation methods for ME/CFS-patients, and to conduct multidisciplinary research in collaboration with Karolinska Institutet, Stockholm. Dr. Indre Bileviciute-Ljungar is particularly interested in complicated clinical pain problems such as patients with chronic fatigue. Her past research concerns mechanisms of pain physiology and neuro-immune communications in experimental pain models. Nowadays she conducts research on neuro-immune communication in patients with fibromyalgia in collaboration with immunologists at Stockholm University, Sweden. Together with multidisciplinary team lead by Dr. Per Julin she is also conducting research on ME/CFS-patients.

Abstract:

ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) is a complex disease characterised by chronic fatigue, post-exertional malaise, sleep disturbances, cognitive failure, pain symptoms, autonomic, endocrine and immune manifestations. The clinical picture of ME/CFS patient is quite complicated and requires a detailed examination as well as exclusion of other diseases or syndromes. Since one year ago a

multidisciplinary team-based clinical project has been started at Dept. of Rehabilitation Medicine, Karolinska Institutet, Danderyd University Hospital, Stockholm, Sweden. The aim of the ME/CFS-project is to improve the diagnosis of ME/CFS patients, to transfer clinical knowledge to the primary care structures, and to establish rehabilitation methods for ME/CFS-patients. The research on ME/CFS from a broad perspective, including assessment, biomarkers, rehabilitation and treatment is also included The multidisciplinary team consists of clinician (1.5 position), medical nurse, physiotherapist, psychologist (1.5 position), social worker and occupational therapist. Three weeks team-based evaluation includes: one visit to the doctor, nurse and social worker; 2 visits to psychologist and occupational therapist and 3 visits to physiotherapist. The ME/CFS diagnosis is based on patient history, subjective and objective findings according to CDC (Fukuda 1994) and Canadian (Carruthers et al 2003) criteria. To exclude other somatic disorders, extended blood and urine analysis as well as polysomnography and 3T brain MRI (including assessment of cerebral blood flow for research purpose) are performed. Moreover, important previous investigations, previous treatment and rehabilitation experiences are also considered.

Since April 2011, the ME/CFS-project had 101 new visits to physician. In 55% of cases (55 patients: 11 male and 44 female) there was a clear indication for further team evaluation because of suspected ME/CFS. After team evaluation 33 patients fulfilled the criteria for ME/CFS: 28 according to Canadian and CDC and 5 only according to CDC-criteria. In cases which did not fulfil the criteria for ME/CFS, other diagnoses were found: 10 cases of chronic psychiatric or neuropsychiatric disorders, and 7 of them together with chronic pain syndrome/fibromyalgia. In 2 cases idiopathic fatigue was explained by chronic sleep disturbances. In 17 cases the previous ME/CFS diagnosis concluded by other clinicians was confirmed by the team, whereas in 11 patients it was given for the first time. It is of interest to note that in 14 cases the existing ME/CFS diagnosis was explained by other disorders either during the first visit to the doctor or after team evaluation.

Altogether, the results of one year multidisciplinary team evaluation show that it is a great advantage to use a multidisciplinary approach in ME/CFS in combination with a thorough medical investigation since the symptoms are very complex and overlap with other disorders that sometimes are very difficult to exclude only by a physician interview/examination and standard laboratory tests. From the clinical point of view a correct diagnosis is of course vital as specific medical treatments or effective rehabilitation techniques exists for many of the other disorders that seemed to mimic ME/CFS, e.g. sleep apnoea, chronic stress-related psychiatric disorders with accompanying pain syndrome, neuropsychiatric disorders, etc. We also believe that a thorough multidisciplinary assessment is beneficial for research purposes, e.g. as a clinical basis for studies of the immunological and CNS patophysiology of ME/CFS, both for diagnostic biomarker- and treatment-studies.

Dr Daniel Peterson

Clinical Research Update 2012

Daniel L. Peterson, M.D., is an internist in Incline Village, Nevada and recognized medical expert on CFS/ME. Dr. Peterson is founder of Simmaron Research, and serves on its Scientific Advisory Board. Dr. Peterson has devoted 25 years of his clinical career to diagnosing and caring for patients with CFS/ME and related neuroimmune disorders, and collaborating with researchers to better understand the illness. Dr. Peterson's repository of more than 1,000 patient biological samples and records is a rich resource for research studies. His experience as both a clinician and a research collaborator provides a unique perspective on CFS/ME for developing translational science. In 2011, Dr. Peterson was appointed Adjunct Professor on the faculty of Health Sciences and Medicine at Bond University in Queensland, Australia.

ABSTRACT:

In spite of many years of intensive research in both the basic sciences and clinical realms, CFS/ME continues to present challenges to scientists and

clinicians with respect to pathogenesis, aetiology, diagnostic criteria and treatment strategies.

Perhaps the greatest challenge to making strides in CFS/ME research is the very nature of this disorder, which is multisystem in scope (both symptoms and pathogenesis); heterogeneous in onset, duration, aetiology; and lacking in specific simple objective and reproducible biomarkers.

Over the past decade, there has been worldwide emphasis on translational medicine to increase the effectiveness of basic research in order to bring appropriate diagnostics and therapies to patient groups in a more cost-effective, orderly, and timely fashion. This philosophical change is reflected in many of the recent studies employed for the study of CFS/ME. Additionally, there has been increased emphasis on integrating informational technology to the study of CFS/ME in order to establish geographically diverse databases and biobanks from which basic researchers as well as clinicians can search, contribute to, and utilize in their respective disciplines.

The CFIDS Association of America has been at the forefront of sponsoring and funding for small pilot projects, particularly seeking innovative approaches to research into CFS/ME with specific timelines and objectives. In 2012, six such studies were selected from a large number of qualified projects and are now underway. These studies will be discussed with respect to study design, objectives, and progress.

The NIH recently sponsored a multi-centered study under the direction of Ian Lipkin at Columbia University to validate the findings of XMRV previously reported by other researchers. The study has now been completed. The multi-centered study design will be presented. Results are expected to be published in the near future.

The Chronic Fatigue Initiative, has designed and supported a multi-centered study, "A Clinical and Biosample Database to Enable Discovery of Pathogens and Pathogenic Mechanisms in Chronic Fatigue Syndrome" to look at an extensive array of clinical aspects of patients with CFS/ME with particular emphasis on patients with acute viral type of onset (duration less than 3 years) versus patients with longstanding illness and classical patients as described both clinically and in the laboratory. A large database is currently being collected with respect to family history, onset, natural history, and associated laboratory findings including serologies, immunological studies, neuroimaging, and functional studies (such as sleep studies, and exercise tolerance tests). Phase 1 of this initiative will evaluate patients and controls for the presence of known human pathogens as well as potential novel agents using the technology available at the Center for Infection and Immunity at the Mailman School of Public Health at Columbia University. This study already has significant enrolment at multiple centers and preliminary results may be available shortly. Phase 2 of the Chronic Fatigue Initiative effort will provide support for investigator initiated projects and access to databases and biobank repositories. Details of the study design, inclusion/exclusion criteria, and timelines will be presented.

There has been increased interest in the study of cerebrospinal fluid due to the multiple neurological symptoms and objective findings by neuroimaging that CFS/ME patients demonstrate. A study looking at cerebrospinal fluid in patients with CFS/ME versus multiple sclerosis patients and normal controls has recently been launched. This project is named “Collaborative Research Using Cerebrospinal Fluid Novel Pathogen Discovery” and will use the technology available at the Center for Infection and Immunity.

In collaboration with Population Health and Neuroimmunology Unit (PHANU) at Bond University in Australia, a pilot project was initiated to evaluate cytokines and microRNA in the spinal fluid. Correlating these findings with peripheral blood with special attention to Natural Killer Cell function and phenotypes may produce clinically relevant biomarkers.

Lastly, a collaborative effort with the acronym CASA (Collection, Aggregation, Storage and Analysis) has recently joined resources of the NIH, CDC, clinicians, and researchers with diverse backgrounds to evaluate by consensus domains of a critical nature to the study of CFS/ME. One of the goals of this collaboration is to establish standards for research in the area of CFS/ME with particular emphasis on determining appropriate tools. These include questionnaires, laboratory studies, histories, and physical examinations which have been validated and recommended for

researchers and clinicians to utilize in research and treatment. The structure of this working group, their goals and objectives and progress to date will be presented.

Dr Andreas Kogelnik

New Paradigms and Collaboration in the Diagnosis and Treatment of ME

Dr Andreas Kogelnik is the Founding Director of the Open Medicine Institute, a collaborative, community-based translational research institute dedicated to personalized medicine with a human touch while using the latest advances in medicine, informatics, genomics, and biotechnology.
The Institute works closely with the Open Medicine Clinic and other clinics to conduct research and apply new knowledge back into clinical practice.

Dr. Kogelnik received his M.D. from Emory University School of Medicine in Atlanta and his Ph.D. in bioengineering/bioinformatics from the Georgia Institute of Technology. Subsequently, he completed is residency in Internal Medicine and a Fellowship in Infectious Diseases at Stanford University and its affiliated hospitals.

Following his clinical training, he remained at Stanford with NIH funding to engage in post-doctoral research in microbiology, immunology and bioinformatics with Dr. Ellen Jo Baron and Dr. Stanley Falkow, where he explored host-response profiles in severely ill patients.

Together with Dr. José Montoya, he was instrumental in the conception, design, and execution of the EVOLVE study - a placebo-controlled, double-blind study of a subset of chronic fatigue syndrome patients with evidence of viral infection.

Dr. Kogelnik worked with Dr. Atul Butte in translational informatics to determine patterns that indicated a high risk for adverse events in paediatric patients at Lucille Packard Children's Hospital.
He is the Medical Director of the Open Medicine Clinic - a community-based research clinic focussed on chronic infectious diseases, neuroimmune disease, and immunology. Dr. Kogelnik has published numerous scientific papers and book chapters, is an Editor of Computers in Medicine and Biology, and is a Consulting Assistant Professor at Stanford University.

With the Open Medicine Institute, he has led the formation of CFS and Lyme Registries and Biobanks as well as creating an infrastructure for providers to collect better data and implement clinical trials across a network of sites.

Abstract not available.

7th Invest in ME
International ME/CFS 1st June 2012
Conference Agenda

Start	Presenter	Presentation
from 07.45	***Registration***	
Futures and Biomarkers		
08.55	**Dr Ian Gibson**	**Welcome to the Conference**
09:05	**Dr Donald Staines**	**Key Note Speech: New directions for ME/CFS Research**
09:45	**Dr Sonya Marshall-Gradisnik**	**Current Knowledge of Immunological Biomarkers**
10:25	**Plenary**	***Questions***
10.35	***Refreshment Break***	
Biological Factors Involved in Chronic Disease and Their Impact on ME Research and Treatments		
10:55	**Professor Hugh Perry**	**An Overview of Neuro-inflammation in Chronic Disease**
11:30	**Professor Maria Fitzgerald**	**Neuropeptides and their role in chronic disease**
12:05	**Dr Mario Delgado**	**Neuropeptides and their role in chronic disease**
12:40	**Plenary**	***Questions***
12.50	***Lunch***	
Clinical Diagnosis and Knowledge sharing		
13:40	**Professor James Baraniuk**	**Systems Biology of Interoceptive Disorders**
14:20	**Dr Øystein Fluge / Professor Olav Mella**	**B-cell Depletion Therapy Using Rituximab in ME/CFS**
15:05	**Plenary**	***Questions***
15.15	***Refreshment Break***	
Clinical Trials		
15:35	**Professor Indre Ljungar**	**One Year Experience of a Standardised Team-based Assessment of Suspected ME/CFS Patients**
15:50	**Dr Daniel Peterson**	**Clinical Research Update 2012**
16:30	**Dr Andreas Kogelnik**	**New Paradigms and Collaboration in the Diagnosis and Treatment of ME**
17:10	**Plenary**	**Dr Ian Gibson - *Questions***
17.30	***Adjourn***	

SUPPORT ME AWARENESS

The BIG CAUSE

Building a future for research into ME

- ME is a neurological disease
- Over 60 outbreaks of ME have been recorded worldwide since 1934
- ME is 3 times more prevalent than HIV/AIDS – it is twice as prevalent as MS
- 25% of ME patients are severely affected - housebound, bedbound
- 25,000 patients are young children
- ME is the largest cause of long term sickness absences from school
- ME does not discriminate, anyone can be affected
- There is no centre of excellence in the UK that treats and researches ME as a physical illness
- UK Charity **Invest in ME** wants to change this with a strategy of biomedical research

Please support our proposal for an examination & research facility for ME in the UK - http://tinyurl.com/2f6gk66

Let the Science Do the Talking

Invest in ME

Charity Nr. 1114035 www.investinme.org Email: info@investinme.org

7th Invest in ME International ME/CFS Conference 2012 1st June 2012 , London