



Chairman, ME Research UK

ME Research Group for Education & support

ME/CFS scientific research: CMO report and beyond

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THE GROUP ON SCIENTIFIC RESEARCH INTO MYALGIC ENCEPHALOMYELITIS (GIBSON PARLIAMENTARY INQUIRY)

“...established to assess the progress of scientific research on M.E., since the publication of the CMO’s Working Group Report into CFS/ME in 2002”

In particular the group has been established to:

- increase public understanding of scientific research into ME/CFS
- evaluate progress in the development of a full programme of research into ME/CFS
- identify research and funding requirements in establishing the cause of ME/CFS”



THE GROUP ON SCIENTIFIC RESEARCH INTO MYALGIC ENCEPHALOMYELITIS

Part I - Progress since CMO report

- Scientific publications

Part II – Specific Reasons for lack of progress

- Case definition
- Influence of the biopsychosocial model
- Biomedical research is patchy and rarely reproduced!

Part III: How can we move forward?



THE GROUP ON SCIENTIFIC RESEARCH INTO MYALGIC ENCEPHALOMYELITIS

Part I - Progress since CMO report

- Scientific publications



THE GROUP ON SCIENTIFIC RESEARCH INTO MYALGIC ENCEPHALOMYELITIS

MEDLINE publications Jan 2002 - May 2006

- **783 documents with CFS as primary focus:**
 - reviews, letters, editorials, commentaries
 - 55 clinical trials
- **57 UK quasi-experimental papers**
 - 36 London Medical Schools
 - 6 Dundee
 - 4 Glasgow
 - 1 Oxford, Whitney, Cardiff, Harefield, Newcastle, Leeds, Nottingham, Aberdeen, Bristol, Southampton, Sidcup



THE GROUP ON SCIENTIFIC RESEARCH INTO MYALGIC ENCEPHALOMYELITIS

MEDLINE publications Jan 2002 - May 2006

783 CFS documents
6231 MS documents
48,110 Diabetes documents

- CFS research is very small scale
- Few “biomedical” studies
- Lots of hypothesis, often novel but with little data to support them



THE GROUP ON SCIENTIFIC RESEARCH INTO MYALGIC ENCEPHALOMYELITIS

Part II – Specific Reasons for lack of progress:

- **Case definition**
- **Influence of the biopsychosocial model**
- **Biomedical research is patchy and generally speaking ignored!**



ME/CFS Biomedical Research: Diagnosis & Case definition?

- **The ME/CFS label:**
 - ME has become a “lay term” used by patients
 - CFS has been adopted by doctors and journals

- **Mis-use of terminology**
 - by mass media
 - patients & doctors

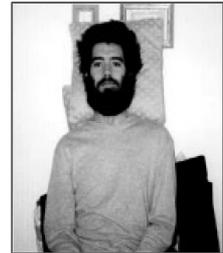


Dame Kelly Holmes has CFS?



Or an overtraining phenomenon?

Matthew Stone (age 24)



Matthew is currently bed bound



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We have an extraordinary situation regarding ME/CFS – there are no biomedical studies on the most severely affected patients

Diagnostic criteria (adults) for “CFS-like” illness 1988–2006

1988 US CDC (Holmes et al)	CFS
1990 London (Dowsett et al)	ME
1990 Australia (Lloyd et al)	CFS
1991 Oxford UK (Sharpe et al)	CFS
1994 US CDC (Fukuda et al)	CFS
2003 Canadian (Expert Consensus Clinical Case Definition)	ME/CFS

**Prior to 1988
Myalgic Encephalomyelitis**

First defined by Acheson, Lancet (1956)

➤ *Occurs in epidemic and sporadic forms*

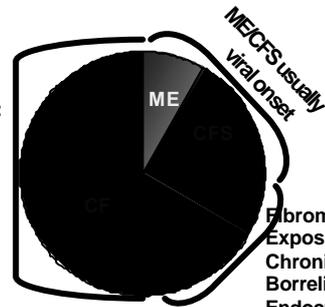
From 1934 - 1990 at least 63 worldwide epidemic outbreaks documented:

- North America – 29
- UK – 16
- Rest of Europe – 11
- Australasia – 4
- Africa – 2
- Asia – 1

Acknowledgement: Dr J.G Parish

1. ME/CFS research: the problem with chronic fatigue

Somataform:
Anxiety
Stress
Atypical
Depression
"lifestyle"
illnesses



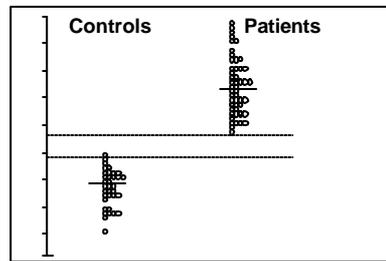
Does any of this really matter?



Source - <http://www.art-teez.org/artact2/art2/vp1.gif>

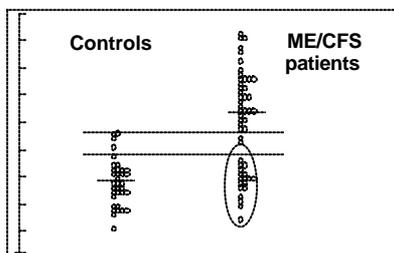
1. ME/CFS research: case definition

This is what we would like to see ...



1. ME/CFS research: case definition

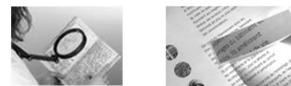
This is what we actually see



CFS/ME research: diagnosis?

Chronic Fatigue Syndrome: The Need for Subtypes
Jason L. *Neuropsychology Review* 2005; 15: 29-58

"This review suggests that there is a need for greater diagnostic clarity and that this might be accomplished by subgroups that integrate multiple variables including genetic, neurological, psychological and biological domains"





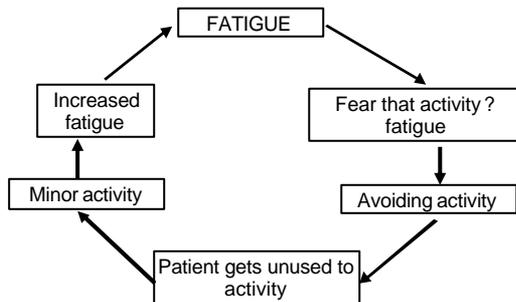
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The biopsychosocial model: evidence for CBT



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RCT's of CBT for CFS patients to 2006

Study	No	Comparison Group	Sessions	Outcome
Huibers MJ, et al 2004	151*	No treatment	5-7	-ve
Risdale et al, 2001	45	Counseling	6	-ve
Lloyd et al, 1993	90	Attend Clinic placebo	6	-ve
Prins et al, 2001	278	Guided support (social worker)	16	+ve
Deale et al, 1997	60	Relaxation	13	+ve
Sharpe et al, 1996	60	"Medical care" (GP follow-up)	16	+ve
Stulemeijer M et al, 2005	71	Waiting list	10	+ve
Bazelmans E et al, 2005	67	Waiting list	12	+ve (just)

Patient Evidence regarding CBT and GET

AfME survey, 2,338 member
 (CMO report appendix 2002)
 93%: CBT had no effect
 79%: reported that they were in severe pain ,
 much or all of the time
 Description

25% ME Group, 437 members (Severely affected analysis report, March 2004)
 93% found CBT unhelpful
 Most so severely ill, unable to attend GP



Medical Research Council

ME/CFS STUDIES

PACE Trial

PACE (Pacing, Activity, and CBT trial)

COST: £3,101,792

Recorded under the "Mental Health in Primary Care" programme in the National Research Register 2004

Description

"CBT based on the illness model of fear avoidance...
 "GET based on the illness model of deconditioning..."

Outline:

A four arm, single blind, randomised controlled trial (600 subjects – OXFORD criteria!!!)



Medical Research Council

ME/CFS STUDIES

FINE Trial

FINE (Fatigue Intervention by Nurses Evaluation)

COST: £1,147,000

Recorded under the "Mental Health in Primary Care" programme in the National Research Register 2004

Description:

"promising new treatment" for ME... designed to increase activity and challenge dysfunctional illness beliefs" (Powell et al, 1999)

Outline:

Three groups: (a) nurse-led self-help (b) supportive listening (c) GP treatment as usual (360 subjects)

MRC

Medical
Research
Council**ME/CFS STUDIES****Funding Record for ME/CFS Projects
Jan 2002-May 2006**

- **PACE trial** **£3,101,792**
- **FINE trial** **£1,147,000**

- **? 7 applications funded, ? any Biomedical**

**THE GROUP ON SCIENTIFIC RESEARCH
INTO MYALGIC ENCEPHALOMYELITIS**

The central point... is that, for patients with chronic fatigue syndrome (and there are some 20,000 members of support groups in the UK alone), the biopsychosocial model offers relatively little, yet it dominates the canvas in terms of research funding and exposure in professional journals instead of being a small part of the overall clinical and scientific picture.

Abbot NC, Spence VA. Lancet 2006; 367:1574

What do other professionals think?

Richard Smith, *Editor. BMJ 2002;324:497-498*

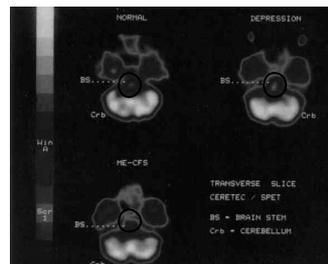
"Many patients have tried CBT and report that thinking differently does not make their disease go away Even so, there is a consensus among patients that if resources were allocated towards rigorous biochemical research it would be more likely to produce a helpful insight into the nature of these diseases, which would be preferable in their eyes to promulgating an incontestable but at the least incomplete paradigm as though it were a cure"

**THE GROUP ON SCIENTIFIC RESEARCH
INTO MYALGIC ENCEPHALOMYELITIS****Part II – Specific Reasons for lack of progress:**

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**THE GROUP ON SCIENTIFIC RESEARCH
INTO MYALGIC ENCEPHALOMYELITIS****Examples of biomedical research findings**

- **Blood flow to the brain**
- **Orthostatic Intolerance**
- **Oxidation**
- **Inflammation**
- **Gene studies**

Brain stem perfusion in ME/CFS

"Brainstem perfusion of 43 ME/CFS patients were significantly lower than controls ($p < 0.0001$) and patients with major depression ($p < 0.005$)"

Costa DC. Brainstem perfusion is impaired in ME/CFS. QJM 1995; 88: 767-73

ORTHOSTATIC INTOLERANCE

The inability to remain standing because of subjective findings (symptoms) or objective findings such as hypotension (signs)



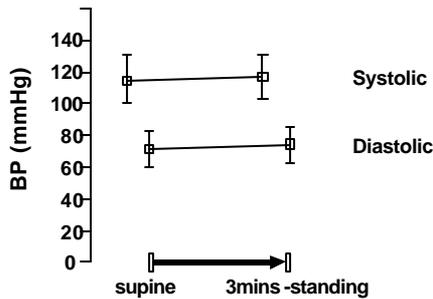
Acknowledgement: Prof J.M. Stewart New York Medical College

What occurs on ME/CFS is simply cardiovascular de-conditioning?

www.kcl.ac.uk/cfs/symptoms.html

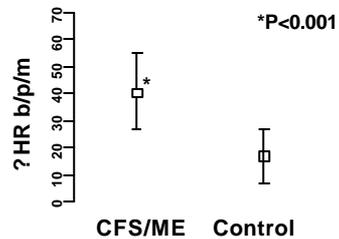
“With cardiovascular de-conditioning there is a drop in BP when standing - this is termed postural hypotension - the reduced blood flow to the brain causes dizziness and sometimes fainting on standing up”

Postural BP change in 31 (14 ♂ 17 ♀) normotensive/non-obese ME/CFS patients

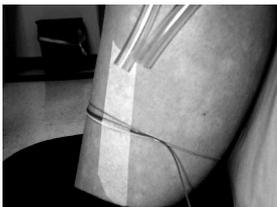


Kennedy & Spence et al. Free Radical Biology & Medicine 2005; 39: 584 – 589

Postural change in heart rate (?HR) in CFS/ME

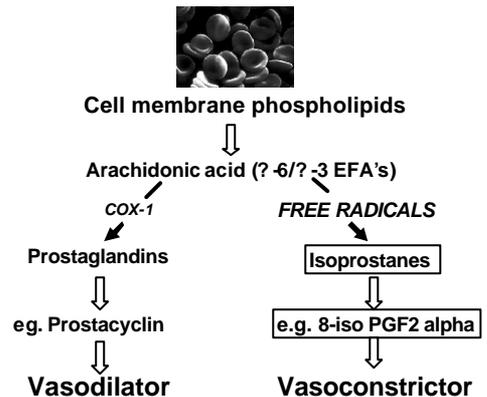


Orthostatic intolerance in ME/CFS



“There is a reduced cardiac output in severe ME/CFS with BP maintained at the cost of restricted flow, possibly resulting in a low flow circulatory state”

Peckerman et al. Abnormal Impedance Cardiography Predicts Symptom Severity in CFS. Am J Med Sci 2003;326:55-60





Original Contribution

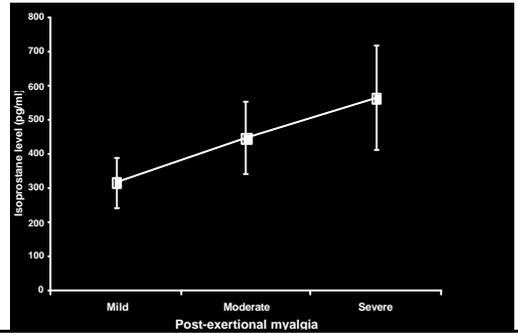
Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms

Gwen Kennedy*, Vance A. Spence, Margaret McLaren, Alexander Hill, Christine Underwood, Jill J.F. Belch

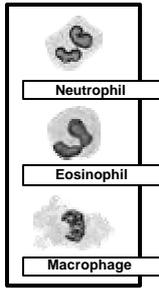
Wander Diseases Research Unit, The Institute of Cardiovascular Research, Ninewells Hospital and Medical School, Dundee, Scotland DD1 9S1, UK

This is the first time that raised levels of the gold standard measure of *in vivo* oxidative stress (isoprostanes) and their association with CFS symptoms have been reported.

Increasing isoprostane levels are associated with post-exertional myalgia



Inflammatory cells significant amounts of oxidation products!



Oxidants Released



- O₂⁻
- H₂O₂
- HOCl
- NO
- ONOO⁻
- NO₂
- HO
- ¹O₂

Research on oxidant-producing inflammatory cells

Increased neutrophil apoptosis in chronic fatigue syndrome

G Kennedy, V Spence, C Underwood and J J F Belch
J. Clin. Pathol. 2004;57:891-893
 doi:10.1136/jcp.2003.015511

Neutrophil apoptosis in ME/CFS

NEUTROPHILS	ME/CFS patients	Controls	p <
Normal Viable cells	63 % (56 - 70)	77 % (71 - 81)	0.002
Early apoptotic cells	32 % (26 - 38)	20 % (16 - 25)	0.002

Van de Putte EM et al. Is chronic fatigue syndrome a connective tissue disorder? A cross-sectional study in adolescents. *Pediatrics.* 2005; (Apr)115:415-22

- No connective tissue abnormality
- No joint hypermobility
- Normal collagen metabolism

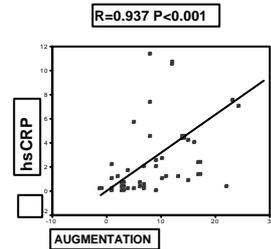
“There is, however, a wholly unexpected finding of stiffer arteries in adolescents with CFS warranting additional investigation”

INDICES of STIFFNESS

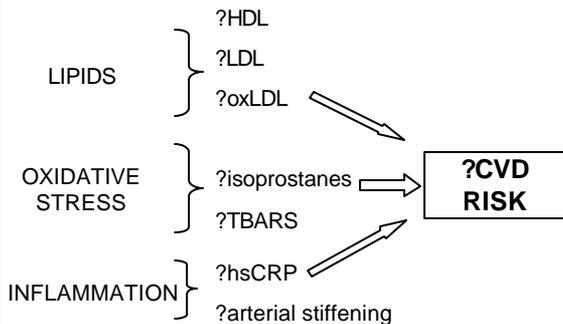
	ME/CFS N=47	Controls N=34	P value
Augmentation (mmHg)	9.5 (6.4)	6.6 (6.6)	0.05
Sub-endothelial viability ratio (%)	166 (32)	196 (30)	0.005
Aortic MAP (mmHg)	119 (18)	105 (13)	0.003

ME/CFS patients have significantly increased arterial stiffness.

hsCRP vs Arterial Stiffness in ME/CFS



Relative risk of a future cardiovascular event in some patients with ME/CFS



Structure of presentation cont.

Part III: How can we move forward?

Strategy for ME/CFS research

**MITOCHONDRIA ! RBC's
IMMUNE CELLS ! MUSCLE
BLOOD VESSELS ! GENES
BRAIN**

neutrophil
eosinophil
macrophage

Integrative Array Analyzer



Current ME Research UK funded biomedical research

Project leader	University	Title of project
Dr Faisal Khan	Department of Medicine, University of Dundee	Further investigations into abnormalities of the ACh endothelium -dependent vasodilator pathway in CFS patients
Dr Gwen Kennedy	Department of Medicine, University of Dundee	An investigation in biochemical and blood flow aspects of CFS in children
Prof Myra Nimmo	Department of Applied Physiology University of Strathclyde	The response of IL-6 and its receptors to a standardised aerobic exercise challenge in CFS patients
Dr Lorna Paul	School of Health and Social Care, Glasgow Caledonian University	Physiological cost of walking at self selected and matched speeds in those with CFS/ME



Current ME Research UK funded biomedical research

Dr. Kishore Bhakoo	MRC Clinical Sciences Centre, Imperial College London	Non-invasive structural and functional neuroimaging in ME/CFS
Dr Julia Newton	School of Clinical Medical Sciences, University of Newcastle	Prevalence of Autonomic Dysfunction in Patients with Myalgic Encephalomyelitis (ME) / Chronic Fatigue Syndrome (CFS).
Dr Lorna Paul	School of Health and Social Care, Glasgow Caledonia University	Evaluation of pain and therapeutic intervention in those with CFS/ME
Dr Les Wood	Department of Physiology, Glasgow Caledonian University	Effects of muscle fatigue on H-reflex excitability in subjects with ME/CFS
Dr John Gow	Dept. of Neurology, Glasgow University	Characterisation of Differential Gene Expression in Patients with CFS/ME



THE GROUP ON SCIENTIFIC RESEARCH INTO MYALGIC ENCEPHALOMYELITIS

The Way Forward: Conclusions

- Doing nothing is not an option
- Thousands of people remain chronically unwell since the CMO report
- The perception that biopsychosocial models are the answer to ME/CFS should be challenged



THE GROUP ON SCIENTIFIC RESEARCH INTO MYALGIC ENCEPHALOMYELITIS

The Way Forward: Conclusions

➤ Expedite the Biomedical Research Agenda by:

- Ring-fencing central funds for basic biomedical research
- Invite “new blood” researchers into the field

Recent gene work is a good example of what can be done IF resources can be found



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 D. Newton PhD
 N.C. Abbot PhD
 J.J.F. Belch MD FRCP

**Vascular & Inflammatory Diseases
 Research Unit
 Department of Medicine
 University of Dundee**



...please help us continue making progress.