IACFS/ME

Dedicated to research, education, treatment and finding a cure for ME/CFS

Biennial International Conference

Translating Evidence into Practice

September 22-25, 2011

Delta Ottawa City Centre Hotel, Ottawa, Ontario, Canada

Conference Syllabus

iacfsme.org

Table of Contents

International Association for
IACFS/ME
Chronic Fatigue Syndrome

International Association for CFS/ME

The mission of the IACFS/ME is to promote, stimulate and coordinate the exchange of ideas related to CFS, ME and fibromyalgia (FM) research, patient care and treatment. In addition, the IACFS/ME periodically reviews the current research and treatment literature and media reports for the benefit of scientists, clinicians and patients. The IACFS/ME also conducts and/or participates in local, national, and international scientific conferences in order to promote and evaluate new research and to encourage future research ventures and cooperative activities to advance scientific and clinical knowledge of these illnesses.

The IACFS/ME shall at all times be organized and operated exclusively for charitable, scientific, literary or educational purposes as a qualified exempt organization described under section 501 (c) (3) of the Internal Revenue code of 1986 and the regulations promulgated there under as they may now exist or as they may be hereafter amended.

IACFS Board of Directors

In Appreciation

The International Association for CFS/ME (IACFS/ME) gratefully acknowledges support from those who support our commitment to education for researchers, clinicians and patients.

Bogoroch & Associates

The Great Plains Laboratory

Marlene Guthrie

McKesson Canada

National ME/FM Action Network

Simmaron Research
Mr. & Mrs. James M. Walton
(In honor of Sue Sausone)

Waterloo Wellington Myalgic Encephalomyelitis Association

Annette Whittemore

Whittemore-Peterson Institute
for Neuro-Immune Disease

UNEVX, Inc

Conference Function and Room Locator

Function	Location
Conference Registration	Lower Level Lobby Foyer
Professional Conference Workshops (Thursday)	Richelieu Room – workshops 2 & 8 Frontenac Room – workshops 4 & 5 Joliet Room – workshops 3 & 6 Capitale Room – workshops 1 & 7 *All four rooms are Conference level*
General Sessions	International Ballroom AB *Lower Lobby Level*
Exhibits – Networking Center	International Ballroom C *Lower Lobby Level*
Poster Presentations - Networking Center	International Ballroom C *Lower Lobby Level*
Breaks, Refreshments – Networking Center	International Ballroom C *Lower Lobby Level*
Patient Relaxation Room	York Room *Convention Level*
Lunch Options	101 Café (hot or cold lunch buffet in the hotel) Tim Hortons (sandwiches,wraps & soups)
IACFS/ME Business Meeting (Saturday)	Frontenac/Joliet Room *Conference level*
IACFS/ME Reception	Panaorama *Top floor*
IACFS/ME Banquet	International Ballroom AB *Lower Lobby Level*
Restrooms	Lower Level Foyer and Convention Level

IACFS/ME Awards Banquet

Saturday, September 24, 2011

Delta Ottawa City Centre

Reception
6:30pm
Panorama Room

Dinner
7:30pm
International Ballroom A-B
Banquet Ticket Required for Admission

Awards Ceremony & Keynote Presentation
8:30pm

Governor Rudy Perpich Memorial Award
Leonard Jason, Ph.D.

Nelson Gantz Clinician Award
Nancy Klimas, M.D.

Junior Investigator Award
Ekua W. Brenu, Ph.D. Candidate

Research Excellence Award
Mary Ann Fletcher, Ph.D.

Special Service Award
Lydia Neilson

Special Service Award
Ellen Piro

Banquet Keynote
Ten Important Facts Derived from M.E./CFS History and That Can Improve M.E./CFS Research
Byron M. Hyde M.D.

Master of Ceremonies
Fred Friedberg, Ph.D., President IACFS/ME

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Foundation for Care Management (FCM) and the IACFS/ME. FCM is accredited by the ACCME to provide continuing medical education for physicians.

FCM designates this educational activity for a maximum of **23** *AMA PRA Category 1 credits* ^{TM}. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The Foundation for Care Management is an approved provider of continuing nursing education by the Colorado Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. Approval period: July 1, 2009—June 30, 2012. Provider # FCM-0612.

Outcome Objectives:

Upon completion of these learning activities on CFS and Fibromyalgia, the healthcare provider should be able to:

1. Discuss the prevalence and incidence and epidemiology of CFS and fibromyalgia.
2. Describe chronic fatigue and fibromyalgia as it exists in different parts of the globe; how different cultural spheres handle these conditions and how research priorities differ in different settings
3. Examine through case studies, discussion, and reflection best practices in caring for patients with CFS and Fibromyalgia.
4. Describe the chronic viral infections and reactivation of virus in chronic illness, methodological issues and the impact on conditions as CFS and fibromyalgia
5. Identify the influence of genes on the pathophysiology in CFS and fibromyalgia, how gene arrays help in integrating multidiscipline data and the potential role of proteomics as a clinical tool.
6. Discuss the definition of CFS and fibromyalgia in children and recommended treatment schemes.
7. Describe the biological causes of fatigue including interactive processes between neuro/immune/endocrine systems in the human body and possible therapeutic interventions.
8. Describe the origins of pain and the best practices in the treatment of pain in fibromyalgia and CFS
9. Describe advances in the assessment and diagnosis of CFS and fibromyalgia
10. Discuss the new developments in pharmacologic treatments for fibromyalgia
11. Identify treatment strategies for sleep problems in people with fibromyalgia and CFS.
12. Discuss the effects of dysfunction in the human brain and the impact on human health in CFS and fibromyalgia.
13. Discuss the influence of genes on the pathophysiology in CFS and fibromyalgia, how gene arrays help in integrating multidiscipline data and the potential role of proteomics as a clinical tool.
14. Apply best practice strategies to appropriately diagnose and treat patients with CFS and/or Fibromyalgia to improve patient outcomes.

Faculty - Oral Presentations

Jose Alegre, M.D
Chief CFS Unit, Vall d'Hebron University Hospital, Barcelona, Spain

Lucinda Bateman, M.D.
Adjunct Clinical Faculty, Departments of Anesthesiology, Family & Preventive Medicine, and Internal Medicine, University of Utah, Salt Lake City, UT, *Director,* Fatigue Consultation Clinic, Salt Lake City, UT

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Voluntary Associate Professor, University of Miami, Miami, FL

Bruce M. Carruthers, M.D., C.M., FRCP(c)
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John K. Chia, M.D.
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Daniel J. Clauw, M.D.
Professor of Anesthesiology, University of Michigan, Ann Arbor, MI

John Coffin, Ph.D.
Research Professor, American Cancer Society, Tufts University, Boston, MA

Kenny De Meirleir, M.D.
Professor of Physiology, Pathophysiology and Medicine, Vrije Universiteit Brussel, Brussels, Beigium

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Derek Enlander, M.D.
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Lina Garcia, M.D.
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Maureen Hanson, Ph.D.
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Leonard Jason, Ph.D.
Professor, DePaul University, Chicago, IL

Benjamin Katz, M.D.
Professor of Pediatrics, Northwestern University, Feinberg School of Medicine, Chicago, IL, *Attending Physician*, Division of Infectious Diseases, Children's Memorial Hospital, Chicago, IL

Betsy A. Keller, Ph.D.
Professor, Ithaca College, Department of Exercise and Sport Sciences, Ithaca, NY

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Chair, Trans-NIH ME/CFS Research Working Group, Office of Research on Women's Health, U.S. National Institutes of Health

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Roland Staud, M.D.
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Conference Planning Committee - Disclosure

Fred Friedberg, Ph.D.	Grants / Research Support: NIH Grant 2008-2011
Kenneth Friedman, Ph.D.	No Significant Disclosure
Staci R. Stevens, M.A.	No Significant Disclosure
Rosamund Vallings, MNZM, MB BS	No Significant Disclosure

Faculty Oral Presentations - Disclosure

The following faculty intend to reference unlabeled/unapproved uses of drugs or products in their presentation

Jose Alegre, M.D
John K. Chia, M.D.
Jose Montoya, M.D.
David R. Strayer, M.D.

The following faculty have disclosed a financial interest or affiliation with one or more of the commercial organizations offering financial support, equipment, or educational grants for this Continuing Medical Education activity, or the IACFS/ME and commercial organizations which do not support this activity but in the interest of full disclosure wish to make attendees aware of a relationship which should be considered in evaluating individual presentations.

Jose Alegre, M.D	Intellectual Property Rights: Instituto Grifols, S.A.
Lucinda Bateman, M.D.	Pharma Sponsored Clinical Drug Trials: Pfizer, Forest, Eli Lilly, Hemispherz Biopharma. Consultant: Pfizer, Speakers Bureau: Eli Lilly, Forest, Pfizer. Have applied for grants from NIH and a Private Instution for CFS Research although not given at this time.
Roumiana S. Boneva, M.D., Ph.D.	Grant / Research Support: Unidentified Government Source
Ekua W. Brenu, PhD candidate	Grant / Research Support: Mason Foundation, Alison Hunkr Foundation, Queensland Australia Government
Gordon Broderick, Ph.D.	Grant / Research Support: U.S. National Institutes of Health, U.S. Department of Defense, CFIDS Association of America
Bruce M. Carruthers, M.D., C.M., FRCP(c)	Consultant: ME/FM Action Network
John K. Chia, M.D.	Grants / Research Support: EV Med Research
Daniel J. Clauw, M.D.	Grants / Research Support: Forest Laboratories, Merck & Co. Consultant: Cypress Biosciences, Eli Lilly, Forest Laboratories, Jazz Pharmaceuticals, Merck & Co, Pierre Fabre Pharmaceuticals USA, Pfizer Inc., UCB, Inc.
Derek Enlander, M.D.	Grants / Research Support: Merriman Foundation
Fred Friedberg, Ph.D.	Grants / Research Support: NIH Grant 2008-2011
Lina Garcia, M.D.	Grants / Research Support: NIH
Leonard Jason, Ph.D.	Grants / Research Support: NIH
Benjamin Katz, M.D.	Grants / Research Support: NIH
Betsy A. Keller, Ph.D.	Grants / Research Support: NIH (grant collaborator)

Nancy Klimas, M.D.	Grants / Research Support: Department of Defense, Veterans Administration, NIH, CFIDS association, Private Donations, Employment: VAMC, University of Miami
Anthony L. Komaroff, M.D.	Grants / Research Support: NIH Grant Pending not yet awarded
Christine Kozak, Ph.D.	Grants / Research Support: Intramural Research Program of the NIH, NIAID
Charles W. Lapp, M.D.	Grants / Research Support: Chelsea Therapeutics, Pfizer, Consultant: Pfizer, Stock Shareholder: Hemispherx Biopharma, Speakers Bureau: Pfizer, Forest, Lilly Pharmaceuticals
Judy Mikovits, Ph.D.	Grants / Research Support: NIH-NIAD
Andrew H. Miller, M.D.	Grants / Research Support: Johnson & Johnson (Centocor), Glaxo SmithKline, Schering Plough Research Institute, Consultant: Abbott Laboratories, AstraZeneca, Glaxo SmithKline, Lundbeck Research USA, Hoffmann-La Roche, Wyeth/Pfizer Inc., Schering Plough Research Laboratories (now Merck)
Harvey Moldofsky, M.D., Dip.Psych., FRCPC	Grants / Research Support: Tonix, Consultant: Tonix Pharmaceuticals, Pfizer, Eli Lilly, Jazz Pharmaceuticals
Christopher R. Snell, Ph.D.	Other Material Support: University of the Pacific, CFS Advisory Committee
Roland Staud, M.D.	Grants / Research Support: NIH, Pfizer, Forrest Pharmaceuticals
Lea Steele, Ph.D.	Grants / Research Support: U.S. Department of Defense, Other Material Support: Baylor University
David R. Strayer, M.D.	Consultant & Employment: Hemispherex Biopharma, Inc.

The following faculty reported that they had no financial interest in any products or services to be discussed.

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McMaster University

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Medical Scientific Group of the Circle of Friends of Bruno Groening, Talmassing, Germany

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AGENDA - Thursday, September 22
IACFS/ME Professional Workshops

Morning Session: 9:00 am- 12:00 pm

Workshop 1
How to Apply for Grants
Dennis F. Mangan, Ph.D.
Chair, Trans-NIH ME/CFS Research Working Group, Office of Research on Women's Health, U.S. National Institutes of Health
Cheryl L. McDonald, M.D.
Medical Officer, National Heart, Lung and Blood Institute, U.S. National Institutes of Health

Workshop 2
Treating Sleep, Pain and Fatigue in ME/ CFS Patients
* *This workshop will be repeated in the afternoon session*
Charles W. Lapp, M.D.
Associate Clinical Professor, Duke University Medical Center, Charlotte, NC
Medical Director, Hunter-Hopkins Center, Charlotte, NC
Lucinda Bateman, M.D.
Adjunct Clinical Faculty, Departments of Anesthesiology, Family & Preventive Medicine, and Internal Medicine, University of Utah, Salt Lake City, UT, *Director,* Fatigue Consultation Clinic, Salt Lake City, UT

Workshop 3
Pediatrics and CFS/ME
Rosamund Vallings, MNZM, MB BS
Board Member, IACFS/ME
Family Physician, Howick Health and Medical Clinic, Auckland, New Zealand
Teruhisa Miike, M.D, Ph.D.
Board Member, IACFSME
Chief, Hyogo Children's Sleep and Development Medical Research Center, Hyogo, Japan

Workshop 4
Fibromyalgia Theory and Practice
Daniel J. Clauw, M.D.
Professor of Anesthesiology, University of Michigan, Ann Arbor, MI
towards "personalized analgesia" for the chronic pain patient

12:00 pm - 1:30 pm
Lunch Break/Visit Exhibits
Note: Lunch is Self Pay from hotel and local restaurants

Afternoon Session: 1:30 pm – 4:30 pm

Workshop 5
Behavioral Assessment and Treatment of ME/CFS
Fred Friedberg, Ph.D.
President, IACFS/ME
Research Associate Professor, Stony Brook University, Stony Brook, NY
Leonard Jason, Ph.D.
Professor, DePaul University, Chicago, IL

Workshop 6
Exercise Intolerance: Guide to Management and Treatment
Staci R. Stevens, M.A.c
Vice President, IACFS/ME, *Founding Executive Director*, Fatigue Lab, University of the Pacific, Stockton, CA
Christopher R. Snell, Ph.D.
Professor, Department of Sport Sciences, University of the Pacific, Stockton, CA
J. Mark VanNess, Ph.D.
Associate Professor, Department of Sport Sciences, University of the Pacific, Stockton, CA, *Adjunct Professor*, Department of Bioengineering, University of the Pacific
Adjunct Instructor, Department of Biology, University of the Pacific
Brian D. Moore, Ph.D., ATC
Assistant Professor, Sport Sciences Dept, University of the Pacific, Stockton, CA

Workshop 7
Fibromyalgia Assessment and Treatment
Roland Staud, M.D.
Professor, University of Florida, Gainsville, FL

Workshop 8
Treating Sleep, Pain and Fatigue in ME/ CFS Patients
Charles W. Lapp, M.D.
Associate Clinical Professor, Duke University Medical Center, Charlotte, NC, *Medical Director*, Hunter-Hopkins Center, Charlotte, NC
Lucinda Bateman, M.D.
Adjunct Clinical Faculty, Departments of Anesthesiology, Family & Preventive Medicine, and Internal Medicine, University of Utah, Salt Lake City, UT, *Director,* Fatigue Consultation Clinic, Salt Lake City, UT

AGENDA – Friday, September 23

10th International IACFS/ME Biennial Conference

Translating Evidence into Practice

8:30 am - 8:45 am
Welcome and Introduction
Fred Friedberg, Ph.D.
President, IACFS/ME

8:45 am - 9:15 am
Plenary Session: Gammaretroviruses of Mice and Their Links to Prostate Cancer and CFS/ME
Christine Kozak, Ph.D.

Paper Sessions *following all the papers, the panel members will field questions written on cards by the audience and given to the chair as time permits.*

9:15 am – 10:30 am
Session: Virology Research
Session Chair: Jose Montoya, M.D.

Blood XMRV Scientific Research Working Group: Latest Findings
Graham Simmons, Ph.D.

Detection Of Anti-XMRV Antibodies In Serum of CFS Patients and Healthy Blood Donors in Belgium
Kenny De Meirleir, M.D.

Detection of MLV-like Gag Sequences in Blood and Cell Lines Incubated With Plasma From CFS Patients and Controls
Maureen Hanson, Ph.D.

Chronic Fatigue, Nonrestorative sleep, Musculoskeletal Pain, and Depression in a Disabled Cohort of Survivors of Acute SARS Viral Disease
Harvey Moldofsky, M.D., Dip.Psych., FRCPC, FAPA

10:30 am – 10:45 am
Break / Visit Exhibits

10:45 am - 11:45 am
Session: Virology Research and Review
Session Chair: Jose Montoya, M.D.

Role of the Immune Response in CFS
Jose Montoya, M.D.

The Case FOR Human Gamma Retroviruses (HGRV) in CFS/ME
Judy Mikovits, Ph.D.

*The Case AGAINST Human Gamma Retroviruses (HGRV) in CFS/*ME
John Coffin, Ph.D.

11:45 am – 12:30 pm
Session: Treatment Advances
Chair: Eleanor Stein, M.D.
Health/Performance and Response Status of XMRV/pMRV Antibody Positive vs. Negative Chronic Fatigue Syndrome (CFS) Subjects in a Phase III Clinical Trial
David R. Strayer, M.D.

Rifampin Augments the Effects of Oxymatrine/Equilibrant (oxm/equi) In Patients with Myalgic Encephalomyelitis/CFS
John K. Chia, M.D.

Brief Self- Management of UCF/CFS in Primary Care: A Randomized Trial
Fred Friedberg, Ph.D.

12:30 pm - 2:00 pm
Lunch Break/Visit Exhibitors
Note: Lunch is Self Pay from hotel and local restaurants

2:00 pm – 3:00 pm
Session: Fibromyalgia: Are Tender Points Necessary? A Debate
Chair: Lucinda Bateman, M.D.

Tender Points are Important
Roland Staud, M.D.

Tender Points are Unnecessary
Daniel J. Clauw, M.D.

3:00 pm – 3:30 pm
Break / Visit Exhibits

3:30 pm - 5:30 pm
Session: Diagnosing CFS/ME; Difficult Clinical Cases
Session Chair: Nancy Klimas, M.D.
Case Presentations by: Charles Lapp, M.D., Lucinda Bateman, MD, Rosamund Vallings, MNZM, MB BS, Derek Enlander, M.D.

5:30 pm - 6:15 pm
Visit Poster Presentations / Exhibits

6:15 pm - 7:15 pm
Standardizing Data Collection in CFS/ME CASA Project (collection, aggregation, storage and analyses)
Non CME Session
Session Co-Chairs: Elizabeth Unger, M.D., Ph.D. & Dennis Mangan, Ph.D.
Fred Friedberg, Ph.D., Leonard Jason, Ph.D., Nancy Klimas, M.D., Anthony Komaroff, M.D.

AGENDA – Saturday, September 24

10th International IACFS/ME Biennial Conference
Translating Evidence into Practice

8:00 am – 9:30 am
Session: Case Definitions for Research and Practice
Chair: Kenneth J. Friedman, PhD

The New International Consensus Criteria for ME: Content and Context
Bruce M. Carruthers, M.D.

Contrasting Case Definitions
Leonard Jason, Ph.D.

Data Mining
Leonard Jason, Ph.D.

Pathways to Pathogenesis: Standardized Measures of CFS/ME Illness Domains
Elizabeth R.Unger, M.D., Ph.D.

9:30 am – 10:30 am
Session: Identifying Abnormalities in CFS/ME: The Importance of Exercise Challenge
Chair Staci R. Stevens, M.A.

Exercise Testing to Quantify Effects of Fatigue on Functional Capacity in Patients With CFS
Betsy A. Keller, Ph.D.

The Importance of Exercise Challenge
Christopher Snell, Ph.D.

10:30 am - 11:00 am Break/Visit Exhibits

11:00 am – 12:15 pm
Session 9: The Latest Research in Immunology
Chair: Nancy Klimas, M.D.

Natural Killer Cell Number and Function in a Prospective Cohort of Adolescents with Chronic Fatigue Syndrome and Controls Following Mononucleosis
Benjamin Katz, M.D.

Disparities In Innate and Adaptive Immune Cell Activities in Chronic Fatigue Syndrome
Ekua W. Brenu, PhD candidate

Longitudinal Assessment of Adaptive Immune Regulation in Chronic Fatigue Syndrome
Ekua W. Brenu, PhD candidate

Promoter DNA Methylation and Expression of Perforin in CFS and Controls
Virginia R. Falkenberg, Ph.D.

12:15 pm – 1:30 pm
Lunch Break/Visit Exhibits
Note: Lunch is Self Pay from hotel and local restaurants.

12:30 pm – 1:15 pm
Breakout Session: Mainstreaming ME/CFS Researchers and Healthcare Providers into Our Peer Communities
Chair: Kenneth J. Friedman, Ph.D . *Non CME Session*

1:30 pm – 2:30 pm
Session: New Developments in Pediatric ME/CFS
Chair: Teruhisa Miike, M.D, Ph.D.

Linking Lymphocyte Metabolites with Clinical Course in Post-Infectious Fatigue
Gordon Broderick, Ph.D.

A Trial for Prevention of CCFS Onset from The View Point of Sleep Issue
Terusha Miike, M.D., Ph.D.

Therapeutic Outcome by Two-months Intensive Sleep-Wake Circadian Rhythm Treatments in Japanese Children and Adolescents with Chronic Fatigue
Seiki Tajima, M.D.

What is the Natural History of Chronic Fatigue Syndrome in Young People?
Katherine S. Rowe, MBBS, M.D., FRACP

2:30 pm - 3:00 pm
Break / Visit Exhibits

3:00 pm – 4:00 pm
Session: New Developments in Epidemiology
Chair: Kenneth J. Friedman, Ph.D .

Natural History
Leonard Jason, Ph.D.

CFS Knowledge And Illness Management Behavior Among U.S. Healthcare Providers and The Public
Elizabeth Unger, M.D., Ph.D.

Profile of the Patient with Chronic Fatigue Syndrome; Experience with a Population-Based Registry
Jose Alegre, M.D.

4:00 pm - 5:00 pm
Visit Poster Presentations / Exhibits

5:00 pm - 6:00 pm
IACFS/ME Membership Business Meeting

6:00 pm – 7:00 pm
IACFS/ME Social/Cocktails Hour

7:00 pm - 8:00 pm
IACFS/ME Banquet Dinner

8:00 pm – 9:00 pm
Awards Presentation & Banquet Keynote
Ten Important Facts Derived from M.E./CFS History and That Can Improve M.E./CFS Research
Byron M. Hyde M.D.

AGENDA – Sunday, September 25

10th International IACFS/ME Biennial Conference
Translating Evidence into Practice

8:30 am - 10:00 am
Session 12: Research Developments in Genomics and Genetics
Chair: Christine Kozak, Ph.D.

Expression Patterns of miRNAs in Lymphocytes In Patients with Chronic Fatigue Syndrome
Ekua W. Brenu, PhD candidate

Pathway-Focused Genetic Evaluation of Immune and Inflammation Related Genes in CFS
Mangalathu S. Rajeevan, Ph.D.

Gene Expression Of Sensory Ion Channels, Adrenegic Receptors and Cytokines: Potential Biomarkers for CFS and Fibromyalgia
Lucinda Bateman, M.D.

Gene-Exposure Interactions In The Etiology Of Gulf War Illness: Evidence Of Increased Vulnerability to Neurotoxicants in Identifiable Veteran Subgroups
Lea Steele, Ph.D.

Comparing Gene Expression Patterns in CFS and GWI Using the Kerr ME/CFS Platform
Lina Garcia, M.D.

10:00 am – 10:15 am
Break

10:15 am – 11:45 am
Session: Advances in Brain and Neuroendocrine Functioning
Chair: Andrew H. Miller, M.D.

Regional Grey and White Matter Volumetric Changes in Chronic Fatigue Syndrome (Myalgic Encephalomyelitis):A Voxel-Based Morphometry 3T MRI Study
I. H. Treasaden, M.B., B.S., LRCP, MRCS, FRCPsych, LLM

Evidence For Reduced Aldosterone in Persons with Chronic Fatigue Syndrome
Roumiana S. Boneva, M.D., Ph.D.

Interaction of Self-And Illness-Related Cognitive Processing In The Right Anterior Insula of CFS Patients: An fMRI Study
Andrew H. Miller, M.D.

Decreased Basal Ganglia Activation in CFS Subjects is Associated With Increased Fatigue
Andrew H. Miller, M.D.

Assessment of Regional Cerebral Blood Flow in CFS Using Arterial Spin Labeling MRI
Jonathan P. Dyke, Ph.D.

11:45 am – 1:00 pm
Lunch / Visit Exhibits
Networking Lunch - Offering an opportunity for clinicians to network and talk about assessment and treatment issues.

1:00 pm – 2:00 pm
Session: IACFS/ME Clinical Practice Manual: Developing A New Primer
Guidelines Panel
Fred Friedberg, Ph.D., Rosemary Underhill, M.D., Rosamund Vallings, MNZM, MB BS, Alan Gurwitt, M.D.
Leonard A. Jason, Ph.D., Lucinda Bateman, M.D., Kenneth Friedman, Ph.D.

2:00 pm – 2:30 pm
Summary of the Conference
Anthony L. Komaroff, M.D.

2:30 pm
Conference Concludes

ABSTRACTS

IACFS/ME Professional Workshops

Thursday, September 22, 2011

Workshop 1

How to Apply for Grants

Dennis F. Mangan, Ph.D., Cheryl L. McDonald, M.D.

The National Institutes of Health (NIH), part of the United States Department of Health & Human Services, is the primary U.S. Federal agency for conducting and supporting medical research. To realize its mission of extending healthy life and reducing the burdens of illness and disability, NIH funds grants that support the advancement of fundamental knowledge about the nature and behavior of living systems. As you plan, write and then submit an NIH application for a grant, it is important to know some important submission basics, such as what type of application will be needed (paper or electronic) and which forms are necessary, as well as links to contacts, important deadlines, a general timeline, and guidelines for tracking your application through the process. This Workshop will provide a useful overview of the NIH granting application process. Attendees will receive information on both the grant writing as well as how grants are reviewed to determine scientific and programmatic merit. Award fiscal monitoring, reporting and compliance issues will be discussed. Investigators are encouraged to review the NIH website for the fundamentals of grant writing prior to attending the workshop (http://grants.nih.gov/grants/grants_process.htm).

Workshop 2

Treating Sleep, Pain and Fatigue in ME/ CFS Patients

** This workshop will be repeated in the afternoon session*

Charles W. Lapp, M.D. & Lucinda Bateman, M.D.

Two experienced clinicians will discuss current issues in the management of PWCs (Persons with CFS or FM). Using a combination of brief lectures and actual cases, Drs. Bateman and Lapp hope to stimulate engaging discussions about the practical management of sleep, pain, fatigue, orthostatic problems, maladaptive behaviors, and 'whatever.' Attendees are encouraged to bring their questions to the workshop."

Workshop 3

Pediatrics and CFS/ME

Rosamund Vallings, MNZM, MB BS & Teruhisa Miike, M.D, Ph.D.

Workshop will provide an Introduction and brief description of CFS/ME in Paediatrics and will cover an overview of paediatric case definitions and other diagnostic issues: outline of illness severity, principal symptoms, relationship to puberty and immunisations, the importance of setting up a paediatric consultation and getting the parents involved. Attendees will walk through the patient evaluation process focusing on making the diagnosis taking into consideration such factors as history, psychological evaluation, physical examination, laboratory testing and other investigations. Discussion on diagnosis leads to the development of a Management / Treatment Plan with considerations for Lifestyle (including exercise, stress and dietary approaches), Addressing specific symptoms (sleep, pain, orthostatic intolerance etc.), Medication options, Counselling (child and family). Children diagnosed with CFS/ME will have special Educational needs such as Home-schooling, part-time attendance, material for teachers, travel and coping with exams and special social needs such as Social needs, interaction with peers, sports, other activities and the use of Parent and peer support groups to help cope. Discussion will conclude with a discussion on psychological effects on paediatric patients and their families, masked depression, suicide risk, isolation and family dynamics and conclude with a discussion of related conditions such as fibromyalgia, migraine, polycystic ovaries, and irritable bowel.

Workshop 4

Fibromyalgia Theory and Practice

Daniel J. Clauw, M.D.

The workshop will begin with an overview of the latest research findings in fibromyalgia and related chronic pain states, A particular focus will be on research suggesting that there are different underlying mechanisms of pain that will respond to different types of treatment. Attendees will be taught how to perform a clinical assessment that determines the underlying mechanism(s) of pain that an individual is experiencing, and then base treatment on those underlying mechanisms. The advantages of using combined pharmacological and non-pharmacological approaches will be emphasized. This approach moves towards “personalized analgesia” for the chronic pain patient

Workshop 5

Behavioral Assessment and Treatment of ME/CFS

Fred Friedberg, Ph.D. Leonard Jason, Ph.D.

In this introductory workshop on ME/CFS and FM, participants will learn about practical methods of behavioral assessment and individualized treatment strategies. Our approach consists of self-management focused interventions and non-pharmacologic strategies for clinicians that can offer realistic hope for improvement in these patients. This workshop will benefit clinicians who work with ME/CFS and FM patients.

Workshop 6

Exercise Intolerance: Guide to Management and Treatment

Staci R. Stevens, M.A.C. Christopher R. Snell, Ph.D.

J. Mark VanNess, Ph.D., Brian D. Moore, Ph.D., ATC

This workshop will provide an overview of exercise intolerance and the management of post-exertional symptoms in CFS/ME. A review of assessment tools for measuring physiological responses during exercise will be included, and case studies examining both successes and common failures of persons with CFS/ME will be presented. Given the problem of exercise intolerance in CFS/ME, the workshop will conclude with a practical model that a clinician can use to safely and successfully implement activity management strategies.

Workshop 7

Fibromyalgia Assessment and Treatment

Roland Staud, M.D.

In 2009, a series of publications emerged from a 5-year OMERACT process that evaluated "domains" in FM and treated the syndrome as a distinct disorder. Representatives of industry, FM experts, clinical trialists, attendees, and patients went through a Delphi consensus process and identified and ranked FM syndrome domain constructs, an endpoint that was later voted on by OMERACT attendees, including those with limited expertise in FM. A "preliminary core dataset for clinical trials in fibromyalgia syndrome," based on the domain deliberations, was identified. The core set included pain, tenderness, fatigue, patient global severity, multidimensional function, and sleep disturbance. These core sets underwent a detailed statistical analysis using participants in the National Data Bank for Rheumatic Diseases longitudinal study of rheumatic disease outcomes. The main determinants of global severity and quality of life in FM are **pain, function, and fatigue**. But these variables are also the main determinants in RA and other rheumatic diseases. The content and impact of FM, whether measured by discrete variables or a by a fibromyalgianess scale, seems to be independent of diagnosis. These data argue for a common set of variables rather than disease-specific variables. Current research shows that multidisciplinary pharmacological and non-pharmacological interventions such as antidepressants, exercise and cognitive-behavioural therapy is effective in reducing FM and related symptoms. Physical activity and exercise can improve life quality in FMS patients, increase physical capacity and reduce FM and related symptoms. Furthermore, physical activity appears to increase self-efficacy and self-management. Effective FM treatments include cognitive-behavioral therapy. Current studies do not support the use of passive physical therapies such as massage therapy or manual lymphatic drainage on FMS-symptoms.

Workshop 8

Treating Sleep, Pain and Fatigue in ME/ CFS Patients

Charles W. Lapp, M.D. & Lucinda Bateman, M.D.

Two experienced clinicians will discuss current issues in the management of PWCs (Persons with CFS or FM). Using a combination of brief lectures and actual cases, Drs. Bateman and Lapp hope to stimulate engaging discussions about the practical management of sleep, pain, fatigue, orthostatic problems, maladaptive behaviors, and 'whatever.' Attendees are encouraged to bring their questions to the workshop."

ABSTRACTS

General Session Friday, September 23, 2011

Gammaretroviruses of Mice and Their Links to Prostate Cancer and CFS/ME

Christine Kozak, Ph.D.
Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, Bethesda, MD, 20892-0460, USA

Gammaretroviruses of three distinct host range tropisms have been isolated from the laboratory mouse. These viruses differ in receptor usage, distribution among wild mouse species and strains of laboratory mice, pathogenicity and sensitivity to host restriction factors. Two of these three host range groups, the xenotropic and polytropic mouse leukemia viruses (together termed XP-MLVs) are widely distributed in house mouse species, mice that live in closest contact with humans. XP-MLVs rely on the XPR1 receptor for entry into cells as does the xenotropic murine leukemia virus-related virus (XMRV) initially identified in human patient samples. Despite their initial description as viruses incapable of infecting mouse cells, the xenotropic viruses have the broadest host range of the MLVs. Nearly all nonrodent mammals are susceptible to X-MLVs, as are all wild mouse species and some inbred strains of laboratory mice. Their XPR1 receptor is highly polymorphic, and there are 5 functional variants of *Xpr1* in *Mus* species and laboratory mouse strains that differ in their ability to support entry of XMRV and various isolates of XP-MLVs. The distribution of XP-MLVs and *Xpr1* variants in wild mouse populations provides a good example of how diversifying selection can be driven by genetic conflicts. Restrictive receptor variants evolved in Eurasian house mouse populations exposed to XP-MLV infection suggesting that positive selection favors antiviral alleles in virus-infected species.

The ecotropic and polytropic MLVs have long been linked to disease induction in mice, and the discovery that all wild mice and some laboratory strains are also susceptible to X-MLV has made it possible to examine the disease inducing potential of these viruses in mice as well as in other model systems. X-MLVs are capable of establishing infection in mice carrying permissive XPR1 alleles, but X-MLV does not induce or accelerate disease in mice with permissive receptors inoculated as adults or neonates, and X-MLVs do not readily establish productive infection in monkeys. Host factors that restrict retroviruses effectively limit virus spread and disease induction in mice and other species.

Session: VIROLOGY RESEARCH

Session Chair: Jose Montoya, M.D.

Multi-laboratory Evaluations of XMRV Detection Assays

Graham Simmons, Ph.D.
John M. Coffin[2], Indira K. Hewlett[3], Shyh-Ching Lo[4], Judy A. Mikovits[5], William H. Switzer[6], Jeffrey M. Linnen[7], Francis Ruscetti[8], Simone A. Glynn[9] and Michael P. Busch[1]
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[4]Division of Cellular and Gene Therapies and Division of Human Tissues, FDA, Bethesda, MD 20892, USA
[5]Whittemore Peterson Institute and University of Nevada, Reno, NV 89557, USA
[6]Division of HIV/AIDS Prevention, CDC, Atlanta, GA 30333, USA
[7]Gen-Probe Incorporated, San Diego, CA, USA
[8]Laboratory of Experimental Immunology, National Cancer Institute-Frederick, Frederick, MD 21701, USA
[9]Transfusion Medicine and Cellular Therapeutics Branch, NHLBI, Bethesda, MD 20892, USA

Background:
The Blood XMRV Scientific Research Working Group was established to design and coordinate collaborative studies to investigate the prevalence of XMRV in blood donors using standardized XMRV assays.

Materials And Methods:
A multi-phase study has been designed to evaluate XMRV nucleic acid and serological detection assays in terms of sensitivity, specificity and reproducibility; assess assay performance on various specimen types represented in existing blood donor/recipient repositories, and determine the prevalence of XMRV in blood donors. Phase I involved production of whole blood (WB) and plasma analytical performance panels spiked with XMRV infected cells or virus, respectively. These panels were tested in a blinded fashion using XMRV nucleic acid amplification testing (NAT) developed by seven participating laboratories. Phase II represented pilot studies to compare XMRV detection using frozen PBMCs, WB and plasma derived from individuals identified as XMRV viremic in a previous study. Additionally, serology was performed on plasma by two laboratories. Phase III involves further evaluation of the clinical sensitivity and specificity of candidate NAT, serology and culture assays by using a blinded panel of 15 pedigreed positive samples, together with pedigreed negative samples and spiked positive controls.

Results:
In phase I, all laboratories detected at least 136 proviral copies/ml and 5/7 assays demonstrated even more sensitive limits of detection. 5/7 plasma RNA assays performed similarly, with limits of detection of 80 RNA copies/ml or less. The initial unblinded pilot study in phase II resulted in two laboratories detecting MLV-like sequences in the plasma, but not PBMCs or WB, from all four subjects. A third laboratory detected no viral sequences. A second, blinded, pilot study using the same four subjects and two validated negative controls was less conclusive, with three laboratories detecting no viral sequences with any of the samples. A FACS-based serological assay detected antibodies in 3/4 XMRV-positive individuals, but also in 1/2 negative controls. A western-based assay found no evidence of serology in any sample. Results from Phase III are expected soon.

Conclusions:
The Blood XMRV SRWG has established a collaboration between many of the laboratories conducting research into XMRV and its detection in blood and has initiated steps to compare performance of XMRV assays using analytical and clinical panels comprised of blood samples from XMRV-positive and negative pedigreed subjects.

Detection Of Anti-XMRV Antibodies In Serum of CFS Patients and Healthy Blood Donors in Belgium

Kenny De Meirleir, M.D.
Marc Frémont[2], Svetlana Khaliboulina[3], Vincent C. Lombardi[3], Cassandra Puccinelli[3], Kristine Metzger[2], Judy A. Mikovits[3]
1. Department of Human Physiology, Vrije Universiteit Brussel, Brussels, Belgium
2. RED Laboratories, Zellik, Belgium
3. Whittemore Peterson Institute, Reno, Nevada, USA

Objectives:
Xenotropic murine leukemia virus–related virus (XMRV) is a new human gammaretrovirus originally identified in prostate cancer patients with a deficiency in the antiviral enzyme RNase L. An association has been made between XMRV and Chronic Fatigue Syndrome (CFS), with a 2009 study reporting the presence of XMRV DNA in the blood of 67% of CFS patients, whereas only 3,7% of healthy controls tested positive. In 2010 another study detected murine leukemia virus (MLV)-like GAG sequences in 86,5% of CFS patients, versus only 6,8% of healthy blood donors. A number of other studies, however, have failed to detect XMRV DNA in the blood of CFS patients.
The objectives of this study were to investigate the association between CFS and XMRV in a Belgian population of patients, and to estimate the prevalence of XMRV infections in the general population in Belgium.

Methods:
A flow cytometry-based assay was used to detect the presence of circulating anti-XMRV antibodies in the serum of 84 Belgian CFS patients. A subgroup of these patients (21) have developed CFS after receiving a blood transfusion. Serum obtained from 44 Red Cross healthy blood donors was also tested. Samples were collected in Belgium and sent, blinded, to the Whittemore Peterson Institute in Reno for analysis.

Results:
48 out of 84 patients (57%) presented circulating antibodies against XMRV (10 out of the 21 patients who received a transfusion). In contrast, only 7 out of 44 controls had anti-XMRV antibodies (16%).

Conclusions:
The higher prevalence of serology positives in the patient population, compared to the controls, supports the idea that XMRV is involved in the pathogenesis of CFS. The finding that 16% of healthy blood donors present evidence of infection with XMRV or a related virus raises questions regarding the need to screen blood donors for asymptomatic XMRV infections.

Prof. Kenny De Meirleir, M.D., Ph.D., Department of Human Physiology, Vrije Universiteit Brussel, Pleinlaan 2, B-1051 Brussels Belgium, Email: de.meirleir@telenet.be

Detection of MLV-like gag Sequences in Blood and Cell Lines Incubated With Plasma From CFS Patients and Controls

Maureen Hanson, Ph.D.
L.L. Lee[1], L. Lin[1], D.E. Bell[2], D. Ruppert[3], S. Levine[4], D.S. Bell[5].
[1]Cornell University, Molecular Biology and Genetics, Ithaca NY, [2]State University of New York, Dept. of Medical Anthropology, Buffalo NY, [3]Cornell University, School of Operations Research and Information Engineering, Ithaca NY, [4]Private Practice, New York City, [5]State University of New York, Dept. of Pediatrics, Buffalo NY

Objectives:
To determine whether viruses related to XMRV could be detected in peripheral blood from adult subjects who are either ill with CFS, are recovered from CFS, or have no history of a CFS diagnosis.

Methods:
Subjects were divided into five groups. Ten subjects were severely ill with CFS, ten met Fukuda criteria at one time but now considered themselves recovered, and ten subjects from the same geographic area in Western New York were healthy and had never been diagnosed with CFS. Standard instruments were administered to assess the health status of the subjects in these three groups. An additional ten ill subjects and ten control subjects lacking any CFS history were recruited from a physician's practice in New York City and a different region of upstate New York, respectively. Blood was collected in EDTA tubes and nucleic acids made from PBMCs or whole blood. Plasma was incubated with human cells in culture. Nested PCR with USB Hot-Start IT FideliTaq was

performed with *gag* primers. Any PCR products of expected sizes were sequenced. Samples were tested for mouse contamination with primers to IAP and/or mouse mitochondrial DNA. Control experiments in which human nucleic acid samples were spiked with mouse DNA were performed to determine the sensitivity of the assays for mouse contamination.

Results:
The SF-36 scores of the ten individuals who considered themselves recovered were significantly lower than ten members of the healthy control group from the same Western New York area, according to Hotelling's T2 test. Tukey's multiple comparison of means indicates that there are highly significant differences between the scores of the Western New York "severe" and controls on all 7 instruments. *gag* sequences were detected in CFS subjects' blood as well as in some healthy controls. *gag* sequences were detected that were more similar to the MLV-like sequences reported by Lo et al. (2010) than to the XMRV sequences reported by Lombardi et al. (2009). MLV-like *gag* sequences could be detected in nucleic acids prepared from whole and fractionated blood that were negative for the presence of mouse DNA when sensitive assays were performed. Possible reasons for false positive and false negative results when performing highly sensitive PCR assays will be presented.

Conclusion:
gag sequences were detected by PCR in whole blood genomic DNAs that were negative for mouse IAP and mitochondrial DNA. *gag* sequences similar to polytropic MLVs were obtained. The sensitivity of the PCR assays used requires extreme caution in interpreting results.

Maureen R. Hanson, Ph.D., Liberty Hyde Bailey Professor, Dept. of Molecular Biology and Genetics, Cornell University, Biotech. Bldg., Ithaca, NY 14853 USA. mrh5@cornell.edu

Chronic Widespread Musculoskeletal Pain, Fatigue, Depression and Disordered Sleep in Chronic Post- SARS Syndrome; A Case-Controlled Study

Harvey Moldofsky, M.D., Dip.Psych., FRCPC, FAPA
John Patcai

Background:
The long term adverse effects of Severe Acute Respiratory Syndrome (SARS), a viral disease, are poorly understood.

Methods:
Sleep physiology, somatic and mood symptoms of 22 Toronto subjects, 21 of whom were healthcare workers, (19 females, 3 males, mean age 46.29 yrs.+/- 11.02) who remained unable to return to their former occupation (mean 19.8 months, range: 13 to 36 months following SARS) were compared to 7 healthy female subjects. Because of their clinical similarities to patients with fibromyalgia syndrome (FMS) these post-SARS subjects were similarly compared to 21 drug free female patients, (mean age 42.4 +/- 11.8 yrs.) who fulfilled criteria for fibromyalgia.

Results:
Chronic post-SARS is characterized by persistent fatigue, diffuse myalgia, weakness, depression, and nonrestorative sleep with associated REM-related apneas/hypopneas, an elevated sleep EEG cyclical alternating pattern, and alpha EEG sleep anomaly. Post-SARS patients had symptoms of pre and post-sleep fatigue and post sleep sleepiness that were similar to the symptoms of patients with FMS, and similar to symptoms of patients with chronic fatigue syndrome. Both post-SARS and FMS groups had sleep instability as indicated by the high sleep EEG cyclical alternating pattern rate. The post-SARS group had a lower rating of the alpha EEG sleep anomaly as compared to the FMS patients. The post-SARS group also reported less pre-sleep and post-sleep musculoskeletal pain symptoms.

Conclusions:
The clinical and sleep features of chronic post-SARS form a syndrome of chronic fatigue, pain, weakness, depression and sleep disturbance, which overlaps with the clinical and sleep features of FMS and chronic fatigue syndrome.
Publication: Moldofsky and Patcai: Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study.
BMC Neurology 2011 11:37. See: http://www.biomedcentral.com/1471-2377/11/37

Session: VIROLOGY RESEARCH AND REVIEW

Session Chair: Jose Montoya, M.D.

Role of the Immune Response in CFS

Jose Montoya, M.D.
Abstract Unavailable

The Case FOR XMRV/Human Gammaretroviruses (HGRVs) in ME/CFS

Judy Mikovits, Ph.D.

In 2009 using a classical virology approach of viral isolation and transmission, electron microscopy, serology and PCR, Lombardi et al demonstrated the first isolation of XMRV from blood from patients with chronic fatigue syndrome (CFS) predominately from the west coast of the United States. In 2010, Lo et al. extended these studies by detecting nucleic acids of MLV-related variants in the peripheral blood mononuclear cells of CFS from the northeastern United States suggesting additional strains capable of infecting humans exist. In a study of 300 CFS patients, 13 developed lymphoproliferative disorders. Of those tested, 11/11 were positive for XMRV and 9/9 positive for clonal TCR gamma rearrangements. Spontaneous development of four immortalized B cells lines occurred during culture of cells from CFS patients. Three developed from B cells isolated from the peripheral blood (two of whom had B cell lymphoma) and one from a bone marrow biopsy. The B cell lines have a mature CD20+, CD23+ phenotype and produce infectious XMRV. Virus production occurred despite extensive hypermutation of the proviruses in these cells by APOBEC3G. Therefore, XMRV infection may accelerate the development of B cell malignancies by either indirect chronic stimulation of the immune system and/or by direct infection of the B-cell lineage. Since viral load in peripheral blood is low, these data suggest that B cells in tissues such as spleen and lymph nodes could be an*in vivo* reservoir for XMRV. We have also identified an inflammatory cytokine and chemokine signature that distinguishes XMRV infected CFS patients from healthy controls with 94% sensitivity and specificity. Monitoring immune dysfunction affords the opportunity to begin to understand the pathogenesis of XMRVs. In addition to these data, recent advances in developing tests for detection and characterization of variants of XMRV will be also be discussed

Judy A Mikovits, PhD, Research Director, Whittemore Peterson Institute, University of Nevada, Reno MS 0552, 1664 N Virginia St, Reno NV 89557-0552, phone: 775-682-8264, fax 775-996-7159

The Case AGAINST Human Gamma Retroviruses (HGRV) in CFS/ME

John Coffin, Ph.D.
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Xenotropic MLV-related retrovirus (XMRV) was first reported about 5 in a few cases of prostate cancer, but did not attract much attention until its reported association with a large fraction of chronic fatigue syndrome cases about 2 years ago. The publication of the XMRV-CFS connection created a ripple of excitement and interest in the scientific, medical, and patient communities reminiscent of the reports of the association of another retrovirus—HIV--with AIDS some 25 years previously. However, most of the results of the XMRV paper – isolation of infectious virus from patients, frequent detection of virus in plasma and PBMCs by PCR, detection of antiviral antibodies - remain to be replicated outside of the laboratories that authored the original report despite considerable effort worldwide. Indeed, XMRV is now considered by most virologists to be the consequence of a collection of artifacts originating from endogenous murine leukemia viruses prevalent in laboratory and wild mice.

There are several related, but distinct, issues that need to be considered. First, various mouse (*Mus musculus*) subspecies carry over a hundred different endogenous proviruses closely (>90%) related to XMRV in their DNA. Second, mice are extremely widespread, as is their DNA, which can be found sporadically on laboratory surfaces, as well as contaminants of common reagents and materials. Sensitive PCR assays can detect "XMRV" related sequences in DNA from tiny fractions of one cell. To detect such contamination, we developed a more sensitive assay based on mouse IAP sequences present in thousands of copies per cell. Third, although only a few of the endogenous MLV proviruses encode infectious virus, it has been known since the 1970s that some of them can give rise to virus that can infect human tumor lines when passaged through nude mice. Indeed, A virus identical to XMRV is produced by the 22RV1 prostate cancer line that was derived in just this way. In initial reports, however, XMRV did not appear to be sufficiently similar to known proviruses to have been derived this way. However, we have recently shown that this is exactly how it did arise, but not from infection of the precursor CWR22 xenograft with a single virus, but rather with a recombinant between the progeny of two previously undescribed proviruses found in the nude mice used for passage. Since the predicted recombinant is ancestral to all XMRV isolates, and cannot have arisen more than once, it must have found its way into many laboratories as the 22Rv1 cell line was distributed worldwide and, by means that remain to be worked out, into clinical samples from CFS patients.

Session: TREATMENT ADVANCES

Chair: Eleanor Stein, M.D.

Health/Performance and Response Status of XMRV/pMRV Antibody Positive vs. Negative Chronic FatigueSyndrome (CFS) Subjects in a Phase III Clinical Trial

David R. Strayer, M.D.
Judy A. Mikovits[2], Vamsidhar Vurimindi[1], William A. Carter[1]
[1]Hemispherx Biopharma, Inc., Philadelphia, PA; [2]Whittemore Peterson Institute, Reno, NV

Background:
CFS is a severe disorder consisting of profound fatigue and a variety of other debilitating symptoms that affects up to 4 million Americans. Recently, one of us (JAM) identified DNA from a human gamma retrovirus (XMRV) in 67% of CFS subjects. Evidence also suggested that approximately 50% of the CFS infected subjects mounted a specific antibody response against XMRV (Science 326, 585-589 (2009)). The objective of this study was to compare demographic parameters, health/performance status and response of

XMRV/pMRV antibody positive vs. negative CFS subjects enrolled in a Phase III clinical trial evaluating the safety and efficacy of a toll-like receptor 3 (TLR3) agonist, rintatolimod (PolyI:PolyC_{12}U, Ampligen®).
Materials and Methods:
Two-hundred-eight (208) evaluable subjects, who met the 1988/1994 Case Definitions for CFS, participated in this randomized, placebo-controlled, double-blinded, multicenter study. Only severely debilitated patients were selected for this study. The primary endpoint was exercise treadmill duration. Subjects received rintatolimod (200-400 mg) or an equivalent volume of placebo twice weekly by IV infusion for 40 weeks. Baseline (or earliest available specimen) serum samples from all 208 subjects were analyzed for antibodies directed against XMRV/pMRV.

Results:
Seventy (33.7%) of the 208 CFS subjects were positive for antibodies directed against XMRV/pMRV, while 138 (66.3%) were negative. There was no significant difference in the number of CFS subjects positive or negative for antibody with regard to age, gender, duration of CFS, cognitive dimension (SCL90-R), exercise treadmill duration, or SF-36 vitality score ($p>0.3$). However, the subjects negative for antibody had a lower Activity of Daily Living score (66.9 vs. 71.2, $p=0.010$, ANOVA) and a lower overall activity level based upon a lower activity monitor score (183K vs. 210K, $p=0.033$, ANOVA). The percent of subjects with a $\geq$25% increase in exercise treadmill tolerance (ETT) at Week 40 compared to Baseline was significantly greater for subjects receiving rintatolimod (39%) vs. placebo (23%), $p=0.016$ (2 tailed Fisher's Exact Test). Although, there was a trend for greater improvement in exercise duration with rintatolimod treatment for both the XMRV/pMRV antibody cohorts receiving rintatolimod, the antibody positive subgroup had a greater relative percent of subjects showing a $\geq$25% increase in ETT with rintatolimod compared to placebo than the antibody negative cohort. An analysis of concomitant medications utilized by CFS subjects to help treat symptoms of CFS showed that, when compared to placebo, the rintatolimod treated cohort positive for antibodies had a greater percentage of subjects with a decrease in CFS-related medication use at the end of the study (24%), $p=0.039$ vs. the antibody negative subjects (13%), $p>0.10$.

Conclusions:
These results indicate that approximately 1/3 of the CFS subjects have a detectable immune response directed against XMRV/pMRV and that this antibody positive group may respond more favorably to rintatolimod, an antiviral and immune modulator, than the antibody negative cohort. Additional studies to further evaluate XMRV/pMRV in this CFS population are underway.

Rifampin Augments the Effects of Oxymatrine/Equilibrant (oxm/equi) In Patients with Myalgic Encephalomyelitis/CFS

John K. Chia, M.D.
Andrew Chia. EV Med Research

Rifampin augments the effects of oxymatrine/Equilibrant (oxm/equi) in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). John Chia, Andrew Chia. EV Med Research

Objectives:
Chronic enterovirus infection has been implicated in the immunopathogenesis of ME/CFS. Previously, we demonstrated the benefit of oxm/equi, an herbal immune booster, in 50% of ME/CFS patients. Concomitant administration of rifampin in one patient resulted in flu-like symptoms and ulceration of infected pharyngeal tissues, which was followed by symptomatic improvement and decrease of chronically elevated Coxsackievirus B3, 4 antibodies. We evaluated the adjunctive effect of rifampin in patients who were taking oxm/equi.

Method:
46 patients who fulfilled the CDC criteria for ME/CFS were treated with rifampin 300 mg po bid for 7 days while taking oxm/equi (32 responders and 14 non-responders, duration 1.32±0.86 years). 45 patients treated with oxm/equi without rifampin, and 45 outpatients treated with doxycycline and rifampin for MRSA (methicillin-resistant Staphylococcus aureus) infections served as controls. Laboratory studies including CBC, chemistry panel, CPK were obtained before and during treatment if patient had flu-like symptoms. Cytokine gene expression of peripheral blood was performed before and during rifampin treatment for 10 ME/CFS treatments.

Results:
31/46 (67%) patients developed significant flu-like symptoms lasting few days during or after the one-week rifampin treatment. 23/33 (70%) of responders and 0/13 non-responders had additional improvement of fatigue and other symptoms ($p<0.01$, X^2 test). 21/33 (64%) responders who had taken oxm/equi ≥ 1-2 years were able to discontinue the herbs within weeks or months of flu-like symptoms and remained in remission. 0/45 ME/CFS patients on oxm/equi alone and 0/45 MRSA-infected patients on doxycycline and rifampin developed flu-like symptoms. Laboratory studies showed no significant changes, and gene expression study of 12 cytokines demonstrated increase of TNF-α and IL-1α,ß mRNA while on rifampin and oxm/equi.

Conclusion:
Flu-like symptoms were commonly observed in patients who took oxm/equi concomitantly with rifampin, as compared to controls. Subsequent symptomatic improvement was observed in > 60% of oxm/equi responders. Short course of rifampin may be beneficial in

ME/CFS patients who are responding to oxm/equi. The possible mechanism of enhanced immune response will be discussed and further investigated.

Brief Self-Management of UCF/CFS in Primary Care: A Randomized Trial

Fred Friedberg, Ph.D.
Janna Coronel, MA

Objective:
The objective of this study was to test a brief self-management protocol in a primary care setting, in people with medically unexplained chronic fatigue (UCF) and chronic fatigue syndrome (CFS). An effective self-management plan has the potential (1) to improve the generally poor outcomes for UCF and CFS patients in primary care, (2) to greatly expand the availability of behavioral health care for UCF and CFS, and (3) to reduce medical and behavioral utilization for UCF and CFS. The proposed study is an extension of an efficacious two-session self-management clinical trial for CFS in secondary care (Powell et al., 2001).

The hypothesis was tested that a brief self-management- focused cognitive-behavioral intervention will yield improvements in fatigue, physical and role functioning, and psychological distress in comparison to the two control conditions: standard medical care alone or standard medical care plus an attention control symptom monitoring condition.

Methods:
We tested the efficacy of a two - session self-management-focused cognitive-behavioral intervention in a target sample of 108 persons with UCF or CFS. Participants were randomly assigned to one of three study conditions: (1) standard medical care alone; (2) standard medical care plus a nurse-delivered attention control condition of symptom monitoring; or (3) standard medical care plus a nurse-delivered self-management cognitive-behavioral treatment delivered by a nurse.

Results:
At the three month follow-up, sample sizes were as follows: fatigue self-management (FSM) = 21; Symptom Monitoring (SM) = 26; and Usual care (UC) = 21. Forty percent met Fukuda criteria for CFS. Controlling for age, sex and illness duration at the three-month follow-up assessment, a significant reduction was found on the fatigue severity scale ($p<.05$). No significant changes were found on diary fatigue ratings, the SF-36PF, Beck Anxiety Inventory or the Beck Depression Inventory. Actigraphy significantly declined across all conditions ($p<.05$).

Patient global impression of change (PGIC) ratings were as follows for the three conditions (FSM/SM/UC): Improved (13/ 6/4); Unchanged (5/9/11); Worse (2/5/2). Despite little change on our standard measures, brief interviews with study participants revealed that both worsened and unchanged patients across conditions attributed their PGIC ratings to external negative events or lack of healthy activities, whereas improved patients reported increased awareness of their behaviors and affirmative steps to pursue healthy activities.

Conclusion:
A brief, standardized illness management service for UCF/CFS showed modest improvement in fatigue severity and PGIC ratings. PGIC ratings of improved, unchanged, and worsened overall appeared to reflect different attitudes toward the illness and/or differential exposures to negative major life events. These findings indicate a role for self-management activities in generating improved outcomes.

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Session: FIBROMYALGIA: ARE TENDER POINTS NECESSARY? A DEBATE

Chair: Lucinda Bateman, M.D.

Tender Points are Important

Roland Staud, M.D.

Population studies have demonstrated moderately strong associations (odds ratios range 1.3-3.1) between the presence of pain in a body segment and the presence of tender points within that segment. Further, there is evidence of increasing number of tender points with increasing number of painful segments. The reporting of non-specific pain, aching, or stiffness, is also associated with high tender point counts. Importantly, there is no unique cut off at which local pains and tender points occur concurrently in a widespread form. This is consistent with the observation that fibromyalgia (FM) represents one end of a spectrum of musculoskeletal pain and tender points, and that both traits are continuous in the general population. Tender points have been successfully used for the definition of study populations like fibromyalgia. For clinical purposes, however, tender points seem to provide little mechanistic information about individuals' pain and associated symptoms.

Tender Points are Unnecessary

Daniel J. Clauw, M.D.
Abstract Unavailable

Session: DIAGNOSING CFS/ME; DIFFICULT CLINICAL CASES

Session Chair: Nancy Klimas, M.D.
Case Presentations by: Charles Lapp, M.D., Lucinda Bateman, MD, Rosamund Vallings, MNZM, MB BS, Derek Enlander, M.D.

Nancy Klimas M.D.

Abstract

In this workshop, experts will present difficult cases, and discuss the diagnostic and management implications. Cases may include "look alike cases" that presented with the signs and symptoms of ME, but in fact were found to be caused by another disorder; complex management issues; medication use and medication intolerance and other issues of interest to the practicing clinician. Related conditions such as Gulf War Illness will be included in the case discussion. The workshop will welcome interchange with the clinicians attending the session. Basic scientists may also hear in this discussion some of the issues that trigger further research ideas. Charles Lapp, M.D., Lucinda Bateman, MD, Rosamund Vallings, MNZM, MB BS, and Derek Enlander, M.D. will present cases that will serve as a platform for discussion.

Rosamund Vallings MB BS

Case study - A Cautionary Tale

This is a case study of a female with a long history of Chronic Fatigue Syndrome, which followed a typical relapsing and remitting course over many years. She was often very ill interspersed with bouts of reasonably good health.

She was admitted to hospital aged 60 during a very serious "relapse" and died a week after admission

This study serves to remind us of the importance of ongoing surveillance and the need to focus on other diagnostic possibilities over time.

Lucinda Bateman MD

Case Study Patient 1: 39 year old male attorney who was ill for 15 years with mild CFS, then became unable to work. Healthy and very physically active in youth. Fitness conscious. Married at age 23 in 1993.

1994. First child born. Ankle fracture required surgery. Completed college while working in family business. Family business turmoil. Brother commits suicide. Gradually developed unusual fatigue, frequent sore throat and swollen glands, low grade fevers, then pain in the shoulders and sternum. Became less able to exercise vigorously.

1995-2001: Completed college and law school (PCP said he was "just depressed" and thought the challenge would cheer him up). Two more kids born. Marital discord. Low function at times due to severe fatigue, achiness, sore throats, low grade fevers, hot flashes, night sweats and cognitive difficulties. Missed class often to stay in bed and stayed in bed on weekends. Often too ill to mow the small lawn and other times he could play basketball but end up in bed afterward.

2001-2007: Worked as an attorney. More stable but continued chronic symptoms and reduced activity tolerance. Managed basic work hours, could weights but not aerobic exercise, and continued to have fatigue, achiness, brain fog and night sweats. Diagnosed with hyperthyroidism, post surgical hypothyroidism, hypogonadism, hyperlipidemia and obstructive sleep apnea. All were treated. Compliant with CPAP.

2008: Busy period of work. Wife in hospital. Vestibular neuronitis with severe vertigo. Resolved in a few weeks. After this he was progressively less able to maintain a normal work schedule. Cognitive dysfunction made analytical work difficult. After another negative workup to rule out causes of fatigue, the firm partners encouraged him to apply for medical disability leave. 2 year LTD awarded for depression/anxiety.

2009: Full evaluation was done by a CFS specialist. CFS diagnosis confirmed.

MEDS: Synthroid, Lipitor, Androgel, CPAP

Physical Exam:
BMI 35 (muscular habitus with mild obesity)
BP 138/95, pulse 80, supine; BP 140/95, Pulse 100, standing at 3 min (later BPs 140/90- 150/100)
0/18 fibromyalgia tender points.
Lab: Normal except Vitamin D 22 (subsequently supplemented without improvement)
Does not meet criteria for MDD or any other exclusionary mental health condition.

Symptoms: fatigue and cognitive problems, unrefreshing sleep, headaches, mild myalgia and arthralgia, marked activity intolerance with post-exertion relapse, few infection/immune symptoms. Able to complete ADLs, do light household activities, run light errands 2-3 times in a week, and walk on a treadmill for 5-7 minutes, 3 mph, 2-3 times per week on better days. *He was able to drive the truck to 3 day family hunting trip, but unable to participate [stayed in the campground] and went home early.* Vigorous, sustained physical activity, or intense cognitive tasks result in relapse symptoms of 1-3 days duration. Sad about losing his career and anxious about the financial support of his family.

Does he meet CFS criteria?
Does he have OI/POTS? If so, how should it be treated?
Should his blood pressure be treated with a medication?
Should he be on Lipitor?
How should his metabolic syndrome be addressed?
He is maximizing testosterone to maintain muscle mass. Testosterone levels top normal. Is this OK?
What else can be done for him?

Lucinda Bateman MD

Case Study Patient 2: 25 year old woman with severe CFS/FM. Married 1 year. No children.

Childhood: Born with cord around neck but seemed to recover. Dyslexia in elementary school. Bitten by a monkey in Brazil and got rabies shots.
Youth: Soccer and swim teams. Played violin. Diagnosed with auditory processing disorder.
College: Age 17 in 2003. ROTC Air Force 40 hours/week. Major in aerospace engineering 20 cr hr/ semester. Worked 10 hours/week. 4 hours sleep/night not uncommon.

2004-2005: Gradual onset sleep disturbance, generalized weakness and fatigue, concentration difficulties, abdominal pain. After ROTC boot camp (32 days) she never recovered and developed total body aching.

Spring 2006: Failed many courses due to inability to function. Quit ROTC. Quit school. Tried to go on a mission to Hong Kong. Worsened and came home due to "seizures"[shaking tremor attacks] and worsening pain.

June 2007: CFS/FM Evaluation
Primary symptoms: Abdominal pain, nausea/dizziness (vertiginous and OI), fatigue/weakness, seizure-like episodes when too tired.
Additional symptoms: constant headache, attention/concentration, disturbed sleep, night sweats, sore throats, numbness and tingling (shoulders, arms, feet)

MEDS:
Armour thyroid 15 mg bid (for "fatigue"---later d/c), B12 po, fish oil 1 gm bid, multivitamin

EXAM: BMI 25. BP 90/64 Pulse 72 supine. BP 88/58 Pulse 88 standing at 3 min. Pharynx mildly erythematous with moderately large tonsils. Toes are cool with delayed capillary refill. 11/18 TP

Testing: SF36 scores very low except for emotional well being.

Pain diagram: whole body sparing lower legs.
Symptom scores: 9-10 for pain, fatigue, cognition. 7-8 headache, sleep. 4-6 mood.

2007-2011: Interval diagnoses and treatment
Interstitial cystitis. Dysmenorrhea and chronic pelvic pain. GERD/IBS.
Eczema, allergies, reflux related asthma. Mild.
Neurology, urology, gyn consults. Brain MRI, EEG, Tilt table test, PSG, echo all normal.

CURRENT MEDS: amitriptyline 50 mg qhs (for IC), Savella 100 mg bid (mildly improved pain), zolpidem 10 mg q hs, Lortab 7.5/325 bid PRN, alprazolam 1 mg qd, Vit D, Vit C, Mag, Calcium, multiple vitamin. Push oral fluids and sodium. OCP

MEDICATIONS that were not tolerated or not helpful:
Fatigue: Adderall, Nuvigil, Ritalin
Pain: cyclobenzaprine, desipramine, Lyrica, gabapentin, zonisamide, Cymbalta, tramadol, NSAIDS, APAP
Sleep: melatonin, Lunesta, temazepam, Seroquel, trazodone

Currently able to spend about 1-2 hours out of reclining position daily. Makes jewelry at home.
The only intervention that controls pain is activity limitation.

How can pain be improved?
Can function be improved?
Doesn't get along with in-laws. Should she try to convince them she is a good choice for their son?
Should she pursue her dream of having a family…i.e. get pregnant?
What should she be advised about medications during pregnancy?

Charles W. Lapp, M.D.
Case Study
In this workshop, experts will present difficult cases, and discuss the diagnostic and management implications. Cases may include "look alike cases" that presented with the signs and symptoms of ME, but in fact were found to be caused by another disorder; complex management issues; medication use and medication intolerance and other issues of interest to the practicing clinician. Related conditions such as Gulf War Illness will be included in the case discussion. The workshop will welcome interchange with the clinicians attending the session. Basic scientists may also hear in this discussion some of the issues that trigger further research ideas. Charles Lapp, M.D., Lucinda Bateman, MD, Rosamund Vallings, MNZM, MB BS, and Derek Enlander, M.D. will present cases that will serve as a platform for discussion.

Abstract Unavailable from Dr. Enlander

ABSTRACTS

General Session Saturday, September 24, 2011

Session: CASE DEFINITIONS FOR RESEARCH AND PRACTICE

Chair: Kenneth J. Friedman, PhD

The New International Consensus Criteria for ME: Content and Context

Bruce M. Carruthers, M.D., CM. FRCP(C)

Contents- the general thrust of the 2003 Canadian Consensus Criteria was retained and developed further. Several changes were made- e.g. the 6 month waiting period was no longer required, but left to clinical judgment. The symptom pattern of Post-Exertional- Neuroimmune-Exhaustion (PENE) was kept criterial and further articulated. Symptoms and symptom interactive patterns arising from the following subsystems- neurocognitive, pain processing, sleep disturbances, neurosensory and motor, immune, gastrointestinal, genitourinary and endocrine subsystems as well as energy transport impairments (cardiovascular, microvascular, respiratory, thermostatic homeostasis, intolerance of temperature extremes and stress intolerance) are noted if present. Interactive dynamical pattern matches between PENE symptom patterns and those from pathophysiologial subsystems for individuals and groups of patients are noted for causal projectability over time will be mutually confirmative as real kinds. Modifications for paediatric cases were added.

The past historical context is described as well as future implications of this case definition plus any descendents are discussed regarding future research directions, case segregation, and treatments.

In conclusion, it is hoped that this case definition and its descendents will continue to emphasize both the clinical/epidemiological/research realms of observation and challenge all participants to integrate them into a mutual confirmation/disconfirmation process that characterizes both clinical medicine, epidemiology and science in general.

Contrasting Case Definitions

Leonard Jason, Ph.D.
Abigail Brown, Erin Clyne, Lindsey Bartgis, Meredyth Evans, Molly Brown
DePaul University

Objectives:
There has been considerable debate about what case definition to use with the illness commonly known as CFS. For example, some have speculated that the initial definitions of ME ((Dowsett et al., 1994; Goudsmit et al., 2009; Ramsay, 1988)) and later on the Canadian criteria of ME/CFS (Carruthers et al., 2003) select a group of patients that have more severe functional impairments than the Fukuda et al. (1994) criteria. This presentation contrasts individuals diagnosed with the Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS) Canadian case definition (Carruthers et al., 2003) with those that did not meet these criteria (Non-ME/CFS) but met the Fukuda et al. (1994) chronic fatigue syndrome (CFS) criteria. The study also compared individuals diagnosed with another case definition involving Myalgic Encephalomyelitis (ME) (based on criteria from Dowset et al., 1994; Goudsmit et al., 2009; Hyde, 2007; Ramsay, 1988) with those that did not meet these criteria (Non-ME), but met the Fukuda et al. criteria.

Methods:
The sample of patients had been diagnosed with CFS by the Fukuda et al. criteria and were later categorized as meeting ME/CFS and/or ME criteria.

Results:
In general, the ME/CFS criteria identified a group of patients with more functional impairments and physical, mental and cognitive problems than the Non-ME/CFS criteria. The ME criteria identified patients with more functional impairments, and more severe physical and cognitive symptoms than the Non-ME condition. Katon and Russo (1992) have argued that a requirement of more symptoms to meet criteria could inadvertently select for individuals with psychiatric problems. Similarly, Kroenke (2003) found similar results examining 15 variables within a fatigued sample. It is certainly possible that the differences on so many measures between the ME/CFS and the Non-ME/CFS groups was due to the larger number of symptoms of higher frequency and severity who met the ME/CFS criteria.

Conclusion:
The current CFS case definition of Fukuda et al. (1994) has been used internationally by researchers for over 15 years. It is possible that some patients meeting these criteria do not have core symptoms such as post-exertional malaise or memory/concentration problems. By specifying 7 symptoms as with the ME/CFS criteria or by specifying 4 symptoms with the ME criteria, it may be possible to identify a more homogenous and impaired group of patients. The current study suggests that these other ME and ME/CFS criteria might be used to identify patients with possibly more homogenous and severe symptomatology and functional impairment. Both ME/CFS and ME criteria appear to select a more severe group of patients than those that only meet the Fukuda et al. criteria.

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Data Mining

Leonard Jason, Ph.D.
Beth Skendrovic, Jacob Furst, Molly Brown, Meredyth Evans, Abby Brown
DePaul University

Objectives:
Data mining may be a useful tool in aiding in the diagnosis of ME/CFS. There are many challenges in diagnosing ME/CFS. Some symptoms associated with it are common of other illnesses, and there are competing definitions that investigators may use. More work with data mining in ME/CFS research could aid in further identification of cardinal symptoms, leading to better diagnostic ability. This would also combine an objective, computer driven decision with a physician's medically influenced decision to come up with a better and more reliable way to diagnose and treat ME/CFS. This article contrasts two case definitions for Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS). We compared the empiric CFS case definition (Reeves et al., 2005) and the Canadian ME/CFS Clinical case definition (Carruthers et al., 2003) with a sample of individuals with CFS as defined by the Fukuda et al. (1994) criteria versus those without CFS from a community-based sample.

Methods:
Data mining with decision trees was used to identify the best items to identify patients with CFS. Data mining is a statistical technique that was used to help determine which of the survey questions were most effective for accurately classifying cases as defined by the two case definitions versus others contained by the study.

Results:
The empiric criteria identified 79% of patients with CFS and the Canadian criteria identified 87% of patients with CFS. Items identified by the Canadian criteria had more construct validity. ME/CFS is often thought to include post-exertional malaise and neurocognitive disorders, and both did emerge as predictive factors for the Canadian criteria, but not when using the Reeves et al. (2005) empiric case criteria. In addition, sleeping disorders and pain symptoms, other key symptoms of ME/CFS, did emerge for the Canadian criteria as well as in the immune areas (i.e., sore throat and multiple chemical sensitivities), and this supports evidence for the Canadian criteria. In contrast, the empiric criteria tended to identify more general areas, including less activity, social and role functioning problems, and some pain issues. However, critical symptoms such as post-exertional malaise, neurocognitive symptoms and sleep disorders were not identified as discriminating symptoms with the Reeves et al. (2005) criteria.

Conclusion:
The study's overall findings were that the Reeves et al. (2005) criteria were not as capable of identifying cases from non-cases as the Canadian criteria (Carruthers et al., 2003). The Reeves criteria have been criticized as being more general and broader than the Fukuda et al. (1994) criteria, and the results of this study suggest that these criteria are only able to discriminate 79% of cases from others, whereas the Canadian criteria were able to 87% of cases. In addition, when examining the items selected in both analyses, it is apparent that the Canadian criteria appear to select cardinal and central features of the illness.

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Pathways to Pathogenesis: Standardized Measures of CFS/ME Illness Domains

Elizabeth R.Unger, M.D., Ph.D.

Case definitions are used in at least two different circumstances. First, a case definition, when simply and easily applied, may be used as a substitute for a specific diagnostic test to measure disease in a population. This would be done when use of the diagnostic test is impractical for delivering information in a timely and cost-effective manner. An example of this situation is use of "flu-like illness" determined by telephone interview as a surrogate to monitor seasonal or pandemic influenza. A second circumstance occurs when there is no diagnostic test, and case identification requires the use of specific descriptive measures. This is the current situation with CFS/ME, a complex and heterogeneous disorder likely to involve multiple pathways to pathogenesis. Case definitions are essential for public health agencies to determine burden of illness, for clinicians to appropriately diagnose and manage patients, and for researchers to identify risk factors and the underlying biologic basis for illnesses. Limitations in the ability of case definitions to identify homogenous patient populations could be addressed by standardizing how the definitions are applied, or by narrowing the definitions through increased criteria needed to meet the definition, or both. An alternative approach is to improve measures of illness domains (questionnaires and biologic) to allow patients identified by any case definition to be phenotypically sub-grouped in a way that allows the underlying biology to be discovered.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agency.

Session: IDENTIFYING ABNORMALITIES IN CFS/ME: THE IMPORTANCE OF EXERCISE CHALLENGE

Chair Staci R. Stevens, M.A.

Exercise Testing to Quantify Effects of Fatigue on Functional Capacity in Patients With CFS

Betsy A. Keller, B.A.
Micale, FG
Ithaca College

Objective:
The purpose of this study was to assess the effects of post-exertional malaise (PEM) on functional capacity and anaerobic threshold in subjects diagnosed with chronic fatigue syndrome (CFS).

Methods:
Subjects were 10 females and 2 males (41.3±1.11 yrs) diagnosed with CFS by a physician experienced in the diagnosis of CFS. To induce PEM, each subject completed a maximum exercise test on a cycle ergometer. A second maximum exercise test was performed 24 hrs later to assess the effects of exercise-induced PEM on functional capacity. Maximum oxygen consumption (VO_2max), maximum heart rate (HRmax), anaerobic threshold (AT), maximum workload (Wmax), workload at AT (ATwork), and respiratory exchange ratio (RER) were measured. RER is an objective indicator of substrate utilization and subject effort during exercise.

Results:
Significant decreases from test 1 to test 2 were 13.5% for VO_2max (21.5 to 18.6 $ml \cdot kg^{-1} \cdot min^{-1}$; $p<0.01$), 8 bpm for HRmax ($p<0.01$), 18.8% for AT (12.0 to 9.7 $ml \cdot kg^{-1} \cdot min^{-1}$; $p<0.05$), 9.4% for Wmax (121 to 109 W, $p<0.05$), and 17.3% for ATwork (58.3 to 48.2 W; $p<0.05$). However, there was no change in maximum RER indicating that subject effort was maximum and also comparable during both tests.

Conclusion:
Results indicate that PEM decreased maximum functional capacity by more than 13% to below 5 METS; a level at or below that which is required by many job-related activities and IADLs. To compare, VO_2max in healthy individuals is highly reproducible over days and even months ($r \geq .95$)[1], with a SEM of $\leq 6\%$[1,2]. Thus, for subjects in this study, an expected variation between tests would be ± 1.29 $ml \cdot kg^{-1} \cdot min^{-1}$ in contrast to the observed decrease of 2.9 $ml \cdot kg^{-1} \cdot min^{-1}$. Furthermore, PEM decreased AT to below 3 METS (e.g., light-moderate speed walking), which is a level of many activities considered to be sedentary in nature. Thus, completion of sedentary ADLs and IADLs for those with CFS requires production of energy via anaerobic processes that will further contribute to PEM and exacerbate symptoms of CFS. Since many daily activities fall into the 3-5 MET range, individuals with CFS will exacerbate symptoms associated with PEM simply by completing normal daily activities.

[1]Taylor, HL, Buskirk, E & Henschel, A. (1955). Maximal oxygen intake as an objective measure of cardiorespiratory performance. *J Appl Physiol*, 8, 73-80.
[2]Katch, VL, Sady, SS & Freedson, P. (1982). Biological variability in maximum aerobic power. *Med Sci Sports & Ex*, 14(1), 21-25.

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The Importance of Exercise Challenge

Christopher Snell, Ph.D.

The absence of reliable diagnostic laboratory tests or biomarkers presents significant problems for persons with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), treating physicians, and the ME/CFS research community alike. Typically ME/CFS diagnoses rely on self-report measures. An alternative to this approach is to employ direct, objective multi-system, measures of physical function that may also provide insights to the underlying pathophysiology of ME/CFS. One such methodology is cardiopulmonary exercise testing (CPET). The principles underlying CPET are simple. Physical exertion requires that the cardiovascular system supply oxygen (O2) to active muscles and the pulmonary system remove carbon dioxide (CO2) from the blood. Taxing these systems has the capacity to reveal abnormalities that may not be apparent at rest and thus elucidate the mechanisms underlying exercise intolerance in ME/CFS. Some key measures available from CPET include: maximal aerobic capacity (Peak VO2 or VO2 max); ventilatory or anaerobic threshold (VT); and peak respiratory exchange ratio (RER). CPET permits accurate comparison of subjects across serial exercise tests and should be of prime consideration for any clinical intervention trial with functional endpoints. CPET data also allow for the more reliable interpretation of results when an exercise challenge is used to elicit ME/CFS symptoms. As a quantifiable measure of both physiological stress and effort, CPET enables direct comparison between patients and controls on these measures. CPET also has the capacity to objectively document PEM in ME/CFS patients. A significant change in exercise capacity over consecutive tests, it could be argued, is clear evidence of PEM.

Session: THE LATEST RESEARCH IN IMMUNOLOGY

Chair: Nancy Klimas, M.D.

Natural Killer Cell Number and Function in a ProspectiveCohort of Adolescents with Chronic Fatigue Syndrome and Controls Following Mononucleosis

Benjamin Katz, M.D.
Maurice O'Gorman[2], Deli Wang[3], Cynthia Mears[1], Yukiko Shiraishi[4], Renee Taylor[4]
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Introduction:
Chronic fatigue syndrome (CFS) is a complex condition involving severe fatigue and disabling musculoskeletal and cognitive symptoms. Whether immunologic dysfunction accompanies CFS is controversial. Arguably the most consistent immunologic disturbance associated with CFS is reduced function of natural killer (NK) cells.

Objectives:
We examined NK function in our cohort of adolescents following infectious mononucleosis (IM) and recovered controls matched for age, sex and Tanner stage.

Methods:
Nine adolescents with CFS and 9 matched, recovered controls had blood drawn for NK cell quantitation and functional analysis that was performed blinded at 6, 12 and 24 months following IM. At each time point, NK cell quantification was ascertained by flow cytometry as %CD56+ cells, and NK cell function was determined using K562 cells and 3 different dilutions of patient lymphocytes. NK cell numbers were scored as high, normal or low. NK cell function was scored as normal, low or borderline by pre-determined parameters by an investigator blinded as to the patient's diagnosis. Statistical analysis was conducted using generalized linear mixed model with repeated measurements and linear mixed model with SAS 9.2.

Results:
There were 27 evaluable time points for the CFS patients and 25 for the controls. There was no difference in NK numbers between cases and recovered controls. NK function was significantly higher in case patients with CFS 6 months following IM than in recovered controls (p=0.02).
Conclusion: We could not confirm decreased NK cell function in adolescents with CFS following IM.
Acknowledgement: Funded by R01HD4330101AI from the National Institute of Child Health and Human Development

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Disparities In Innate and Adaptive Immune Cell Activities in Chronic Fatigue Syndrome

Ekua W. Brenu, PhD candidate
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Objective:
Cell specific immune investigations have demonstrated a possible link between Chronic Fatigue Syndrome (CFS) and failure to maintain immunological homeostasis. The most common immune cells with known dysfunction in CFS are cytotoxic cells, Natural killer cells and CD8+T cells. This study examined cytotoxic function and markers in CFS patients at 6 months intervals to determine the stability of these observations over time.

Methods:
90 CFS patients (mean age 46.5yrs ±11.7) and 50 healthy controls (mean age 41.9yrs ± 9.6) participated in the study. Flow cytometeric protocols were used in the assessment of cytotoxic activity and cell phenotypes and RT-qPCR analysis in screening for levels of cytoxic molecules that depict the various cytotoxic pathways. These molecules include, granzymes, perforin, interferon (IFN)-γ and tumour necreosis (TNF-α).

Results:
Preliminary results indicate that compared to the healthy controls, CFS patients demonstrate significant decreases in cytotoxic activity at baseline, at 6 and at 12 months. Additionally, NK CD56 bright cells remained decreased in the CFS participants. Cytotoxic, molecules were also differentially expressed in these cells in comparison to the healthy group.

Conclusion:
This study demonstrates and confirms reduced immune function in patients with CFS. These findings substantiate the use of NK cell cytotoxic function as a potential biomarker for CFS.
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Longitudinal Assessment of Adaptive Immune Regulation in Chronic Fatigue Syndrome

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Objective:
Chronic Fatigue Syndrome (CFS) is known to persist for more than 6 months with a very slow recovery rate. It is not known whether immunological abnormalities in CFS remain stable over time or change during the course of the disease. Additionally cytokine measurements have not been consistent across studies which may be associated with the fluctuating pattern of the disease. This longitudinal study assesses proteins and receptors secreted and expressed by CD4+T lymphocytes in CFS patients over time, at baseline, 6 and 12 months.

Method:
50 CFS meeting the CDC case definition and 30 non-CFS control participants were recruited from two states in Australia. Peripheral blood mononuclear cells were preferentially isolated from whole blood samples collected from participants. The samples were then assessed for the expression of Th1, Th2, Th17 cytokines, IL-1α, IL-1ß and TGF-ß using cytometric bead array and flex set kits.

Result:
At baseline there was an increase in IL-10, TNF-α and IFN-γ in the CFS group compared to the healthy control group. However, after 6 months IL-2 was significantly increased and IL-10 and IL-17A were significantly decreased in the CFS group while after 12 months only IL-2 was observed to be significantly increased in the CFS group.

Conclusion:
These results suggest that the cytokine profile in CFS changes during disease progression. This may be associated with disease severity and/or concurrent environmental stressors. Hence there is a need to match experimental findings with data on clinical disease progression.

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Promoter DNA Methylation and Expression of Perforin in CFS and Controls

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Objectives:
Perforin plays a key role in immune surveillance and several studies report decreased perforin protein and mRNA in peripheral blood of patients with chronic fatigue syndrome (CFS). Factors that modulate gene-environmental interaction and thus the pathophysiology of disease include gene silencing by DNA methylation. The objectives of this study were to determine the pattern of perforin gene methylation in conjunction with perforin gene expression and whether these features were altered in CFS.

Methods:
Subjects (34 CFS and 47 non-fatigued, NF) selected from a population based study underwent the Trier Social Stress Test (TSST), a standardized psychosocial test that induces stress, and is known to influence cortisol secretion. Blood samples were collected prior to (10:30am, T1), and after the TSST (3:05 pm, T2). DNA extracted from peripheral blood mononuclear cells (PBMC) was used to examine site-specific CpG methylation levels in the methylation sensitive region (MSR) of the promoter (sites -876, -776, -744, -720, -691, -670 and -650). This was quantified by bisulfite treatment of DNA followed by pyrosequencing. RNA from PBMCs collected at the same time points was used to quantify perforin mRNA expression
by LightCycler real-time RT-PCR. Total RNA from peripheral blood collected at the same time points was used in the Affymetrix Human Exon Array 1.0 platform.

Results:
Methylation of the MSR ranged from 38%-79% and no differences in CpG site-specific methylation of perforin was detected between CFS and NF at T1 or T2. In PBMC, there was no difference in the perforin expression between CFS and NF at T1 but expression was significantly higher in CFS than NF (1.4 fold, p=0.02) at T2. NF subjects had reduced perforin expression

(0.8 fold, p=0.008) and methylation levels were increased by 4% (range 2.6-4.3, p= 0.01-0.05) at four CpG sites (-876, -744, -691, and -670) at T2 compared to T1. However in CFS subjects, methylation levels were increased by 6% (range 4.7-6.8, p=0.02-0.03) at T2 compared to T1 at two positions (-776 and -744) without a corresponding change in expression. Expression results by real-time RT-PCR and exon arrays were concordant.

Conclusion:
While increased promoter DNA methylation correlated with reduced perforin expression in NF, this relationship was not seen in CFS. The small but statistically significant differences in methylation were detected over the course of the day were different for the NF and CFS groups. Further studies are needed to confirm these results and to evaluate explanations
(changes in cell population, circadian rhythm or stress) for the observed dynamics in perforin DNA methylation and expression.

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Session: NEW DEVELOPMENTS IN PEDIATRIC ME/CFS

Chair: Teruhisa Miike, M.D, Ph.D.

Linking Lymphocyte Metabolites with Clinical Course in Post-Infectious Fatigue

Gordon Broderick, Ph.D.
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Objectives:
Chronic Fatigue Syndrome (CFS) affects between 1 and 4 million individuals and costs an estimated $35 billion per year in lost productivity and health care. As CFS can follow Epstein-Bar virus (EBV) and other systemic infections, our objective was to describe differences in immune activation in post-infective CFS (PI-CFS) patients compared to recovered controls.

Methods:
We studied 301 Chicago-area adolescents prospectively over 24 months following diagnosis of monospot-positive infectious mononucleosis (IM). Cluster analysis of subjects chronically fatigued at 24 months (4.3% of cohort) revealed 3 clinical courses: i) a sustained increase in fatigue after a early partial remission (C1), ii) a monotonic decrease in fatigue (C2), or iii) a slow decrease in fatigue after a peak at 12 months (C3). Cryopreserved samples of peripheral blood mononuclear cells (PBMC) were also recovered from 7 PI-CFS subjects and matched recovered controls. Duplicate gene expression profiles were obtained in these samples using the GeneChip Human Gene 1.0 ST microarray (Affymetrix, Santa Clara, CA). A novel computational method was used to assign probabilities of discrete up and down-expressed states for each gene in every individual sample. These probabilities were then combined to identify consistent representation of known molecular interactions and quantify the activity level of close to 600 cellular pathways catalogued in the National Cancer Institute (NCI)/Nature Pathway Interaction Database (PID) and the KEGG database. Patients and patient groups were then compared statistically on the basis of the estimated activity levels of these pathways.

Results:
Previous analysis of plasma cytokines in this cohort indicated immune signaling anomalies specific to PI-CFS subjects and present to different extents in each fatigue sub-group. Consistent with this, 20% of expressed genes (of 92 with fold change>2, $p<0.05$) supported cell signaling and/or immune function. Close to half however (47%) supported cell metabolic function. Derivation of pathway activity levels in individual subjects greatly reduced the false discovery rates (FDRs) isolating 5 pathways with significantly altered activity in PI-CFS (FDR<0.10, $p< 0.005$). Phenylalanine metabolism and Trk neuronal receptor signaling were significantly suppressed in PI-CFS ($p=0.002, 0.004$; FDR=0.08, 0.09) while starch metabolism, glycolysis and pentose phosphate metabolism were up-regulated ($p=0.000, 0.001, 0.003$; FDR=0.04, 0.07, 0.09). Of these, phenylalanine metabolic activity also supported the separation of fatigue sub-groups, with higher activity being linked to a more favorable prognosis.

Conclusion:
These preliminary results suggest that observed differences in cytokine expression are consistent with altered metabolic activity in circulating lymphocytes in PI-CFS patients. These differences may also inform on the course and underlying causes of this illness.

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A Trial for Prevention of CCFS Onset from The View Point of Sleep Issue

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Objectives:
We have been considering that CCFS has been completed with the following order. 1) In spite of night active modern type daily life, people should keep classical morning active daily life, 2) which causes chronic sleep deprivation, 3) developed failure of neuronal function maintenance, 4) induced the derangement of the biological clock which is important and necessary for a human social life and life itself, 5) resulted neuronal fatigue and loss of neurons,6) these conditions connected with each other, finally complete the failure of the everyday life, 7) resulted in school non-attendance and/or so called CCFS. Therefore we think that we will be able to prevent CCFS by reading sleep deficient sign from everyday life of children.

Methods:
Then we investigated the habit of the sleep-wake rhythm for 5,100 students (ranged 6-15 years of age) in Yawata-city, Kyoto to get actual information to contribute to our purpose. We asked all students to record the consecutive 14 days sleep-wake log and studied following subjects, 1) total sleep time, 2) sleep onset time, 3) wake-up time and 4) sleep-wake pattern. The sleep log was classified into the 8 kinds of patterns, which was made beforehand. (1: holiday sleep supply, 2:short sleep, 3:long sleep, 4:irregular sleep, 5:sleep after get home, 6:sleep fragmentation, 7:overlapping, 8:normal sleep)

Results and Conclusion:
Average bed time (First grader: 9:14, Second 9:15, Third 9:16, Fourth 9:33, Fifth 10:03, Sixth 10:21, Seventh 10:49, Eighth 11:15, Ninth 11:51 pm).. Average rise time (First grader: 6:58, Second 7:01, Third 7:01, Fourth 7:00, Fifth 7:06, Sixth 7:10, Seventh 7:03, Eighth 7:14, Ninth 7:31am). Average total sleep time (First grader: 9.8, Second 9.7, Third 9.7, Fourth 9.5, Fifth 9.0, Sixth 8.8, Seventh 8.2, Eighth 8.0, Ninth 7.7 hrs). In addition we found that prolonged short sleep and irregular sleep pattern are the strong risk factors that suggest a difficulty of performing daily school life, in this study. It is considered that sleep deprivation and irregular life style has a direct connection to the CCFS. According to these data we conceived that it may be possible to prevent CCFS by observing a lifestyle, especially a sleep-wake rhythm of children.

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Therapeutic Outcome by Two-months Intensive Sleep-Wake Circadian Rhythm Treatments in Japanese Children and Adolescents with Chronic Fatigue

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Hyogo children's sleep and development medical research center

Objectives:
In the last two decades, we have reported relationship between biological clock system and childhood chronic fatigue (CCF). Biological clock dysfunction is associated with energy metabolism, immune system and frontal lobe dysfunction. Based on these evidences, we have treated patients with CCF at new medical research center for CCF and developmental disorder since April 2009. Here we show the therapeutic outcome of our first year trial for translating evidence into practice.

Methods:
30 patients (15 boys and 15 girls, age 11 to 25) with chronic fatigue caused by sleep deprivation were admitted in the first year of our center. All patients were treated for 8 weeks with bright light therapy, thermal therapy, medication, cognitive behavioral therapy and lifestyle teaching. Self-sleep-logs (S-log) have been recorded during hospitalization. 48hr core body temperature (CBT) monitoring was performed at the beginning and the end of therapy. Delay of circadian rhythm (≥60min.), poor daily variation (ΔCBT<1.0°C) and totally high CBT (1.0°C higher than control) were detected in CBT recordings. Long total sleep time (≥10hr), delayed sleep phase (sleep onset later than 24:00), irregularity of sleep onset and offset (larger variation than 90min.) and sleep segmentation (segmented more than 7 days per 2 weeks) were also detected in S-log recordings. With or without these factors were compared between the beginning and the end of therapy using fisher's exact test.

Results:
Delay of CBT circadian rhythm ($p<0.01$), long total sleep time ($p<0.0001$), delayed sleep phase ($p<0.05$) and irregularity of sleep onset and offset ($p<0.0001$) were significantly improved at the end of therapy.

Conclusion:
Intensive sleep-wake circadian rhythm treatments were effective to improve circadian rhythm. However, recoveries of other chronic fatigue related symptoms and poor performances were insufficient at the time of discharge. Therefore, just a part of patients has resumed normal activity yet. Recovery from sleep disturbance is not the goal but the first stage of improvement for the patients with chronic fatigue. From this point of view, more clinical trials will be needed.

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What is the Natural History of Chronic Fatigue Syndrome in Young People?

Dr Katherine Rowe,
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Objectives:
To follow up consecutive patients referred to the CFS clinic at the Royal Children's Hospital between 1991 and 2009 regarding their level of functioning, self-reported perception of recovery, duration of illness and the usefulness of management strategies.

Methods:
Seven hundred and eighty eight young people age 6-18 years (mean 15 years) (M:F 1:3), were referred from family doctors or consultant pediatricians for diagnosis and management or secondary consultation. Diagnosis required a defined onset over hours or days of persistent or relapsing, debilitating fatigue, which was exacerbated with exercise and did not resolve with bed rest, duration of illness greater than 6 months, and fulfilling the criteria of Holmes et al (1988) and Fukuda et al., (1994). Standardised historical, symptom and psychological data were obtained from 398 and standardised history only, from an additional 390. 398 were followed up prospectively with questionnaires approximately each 2 years, while the second group were contacted by phone during 2010 and 2011, and a questionnaire sent if consent was obtained. The follow up questionnaire recorded functional outcomes, demographics, duration of illness, use of alternative health practitioners and reported usefulness of management strategies.

Results:
Questionnaire follow up data were obtained on at least one occasion for 342 of the 398 (86%). Six occasions between 1996 and 2008 provided 804 returns allowing more accurate timing of reported recovery with multiple data points. 78% of the additional 390 were able to be traced and provided information. The follow up for both groups ranged from 1.7 years to 21 years. The average duration of illness was reported as 5 years with range 1-15 years. By 5 years 60% reported recovery. By 12 years, 88% reported recovery (n=256), although in approximately 1/3 there was an indication that they were conscious of monitoring their workload. Less than 5% were not either studying or working part or full time, often due to other factors than CFS. Many had married (n=38) and those with children (n=15) reported being well. 90% completed or intended to complete post-secondary training. The only alternative practitioners that were deemed helpful were those that provided some relief for muscle pain with massage, or who provided good dietary advice. Restrictive diets and supplements did not reach placebo levels of response. Symptom management and the strategy of balancing social contact, physical activity, educational input and a commitment to regularly attend at least one activity each week as the most useful assistance. Every young person devised a different balance of activities and program depending on severity of illness, stage of education, family circumstances and life interests. Engagement in education was best predictor of functional outcome.

Conclusion:
The outcomes for young people in Australia are generally positive although prolonged. Ongoing support particularly in navigating the education system was highlighted by them as an essential contributor to the quality of their life and their ability to cope.

Session: New DEVELOPMENTS IN EPIDEMIOLOGY

Chair: Kenneth J. Friedman, Ph.D.

Natural History

Leonard Jason, Ph.D.
DePaul University Nicole Porter, Jessica Hunnell, DePaul University, Alfred Rademaker, Northwestern University, Judith A. Richman, University of Illinois, Chicago.

Objectives:
Despite growing knowledge about long-term predictors of chronic fatigue syndrome (CFS) outcomes, many follow-up studies are not prospective in that they either rely on retrospective self-report at a single point in time or they consist of longitudinal data that are analyzed in a cross-sectional manner without taking into account the influence of baseline findings. Clearly, there is a need for more research on the incidence and course of CFS in ethnically and socioeconomically diverse, community populations.

Methods:
The present project was carried out in two stages. In Stage 1, we attempted to re-contact the 213 adults who were medically and psychiatrically evaluated from 1995-1997. These adults were previously evaluated in our original Wave 1 CFS epidemiology project (Jason, Jordan et al., 1999). Stage 2 of the study encompasses a structured psychiatric assessment and a complete physical examination and a structured medical history. The original Wave 1 sample is a stratified random sample of several neighborhoods in Chicago specifically selected to contain individuals from different ethnic and socioeconomic profiles. Although the CFS group had a high rate of follow-up, those in the other groups were much more difficult to track over time. Fortunately, we did not find significant sociodemographic differences at Wave 1 between those we retained in the sample versus those that we were not able to re-contact, and this provides support for the generalizability of the outcomes to the larger sample.

Results:
The study's major finding was that rates of CFS appear to have been relatively stable over the period of time from Wave 1 to 2. As rates of CFS were .42% in Wave 1 (Jason, Richman et al., 1999), estimates from our current natural history study suggest that these rates have stayed relatively constant over the past decade. Sixty-seven percent of participants with CFS at Wave 1 continued to have CFS in our sample at Wave 2. Of the new cases of CFS over time, 75% came from the ICF group, suggesting that this group is at higher risk of developing CFS. In addition, 50% of the remitters went from a CFS diagnosis to the ICF group, indicating that while remitters no longer met CFS case definition, half were still suffering from chronic severe fatigue. Among all the variables in this study, only for post-exertional malaise did the CFS group significantly differ from the other conditions. This reaffirms the

importance of this being a cardinal and critical symptom for CFS, and all of the individuals in the CFS group had this symptom either at Waves 1 or 2. Finally, a high level of mortality was found (18% of those with medical or psychiatric exclusions group, 12.5% for the CFS group).

Conclusion:
There are few studies that have been able to provide estimates of long term CFS outcomes, particularly in culturally diverse, community-based samples. In the present 10 year natural history study, the CFS group for the most part remained rather ill over time.

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CFS Knowledge And Illness Management Behavior Among U.S. Healthcare Providers and The Public

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Dana J. Brimmer, Ph.D., MPH, Roumiana S. Boneva, James F. Jones, , Centers for Disease Control and Prevention

Objectives:
Chronic fatigue syndrome (CFS) is a challenge because of unknown etiology and diagnostic biomarkers, and treatment relies on symptom management. Previous research has shown positive CFS knowledge, attitudes and beliefs among physicians and awareness among the public. We compared CFS knowledge and illness management behavior between healthcare providers (HCP) and the public in order to identify gaps and need for educational interventions.

Methods:
We used DocStyles, a 2009 web-based panel survey of primary care physicians, OB/GYNs, pediatricians, dermatologists, and nurse practitioners, and HealthStyles, a 2010 public consumer mail survey to ask questions about CFS knowledge and illness management behavior. The HCP sample is drawn from an opt-in, verified Epocrates Honors panel. HealthStyles used stratified random sampling to match the national population on region, income, age, and household size. Both surveys asked about CFS awareness, CFS symptoms, and if CFS is a medical or psychiatric condition. HCP were also asked if they have ever made a CFS diagnosis and how they treat and manage CFS. HealthStyles respondents were asked if they knew someone diagnosed with CFS, and then also if they or someone they knew thought they had CFS, what they would do to find out more about the illness.

Results:
The response rate was 46% for DocStyles and 67% for HealthStyles with a sample size of 2,000 and 4,184 participants, respectively. Males comprised 65% of DocStyles physicians and 48% of the HealthStyles sample. Among HCP, 94% heard of CFS compared to 57% of the public. HCP had two to three times higher recognition rates on eight CFS symptom criteria as compared to the general public. When asked if CFS were both medical and psychiatric, 71% of HCP agreed as compared to 30% of the public. Two percent of the public considered CFS a psychiatric condition vs 14% of HCP. A higher proportion of the public considered CFS a medical condition: 27% vs 8% of HCP. Uncertainty whether CFS was either a medical or a psychiatric condition was higher among the public (42%) compared to HCP (8%). Thirty-seven percent of HCP reported ever making a diagnosis of CFS and nearly 10% of the public knew someone diagnosed with CFS. HCP who reported ever diagnosing CFS were more likely to categorize CFS as a medical condition (Chi-square = 98.6, $p<0.01$). Top three ways in which HCP manage CFS were: referring to a medical specialist (35%), prescribing medications (29%), and referring to a psychologist (26%) or prescribing graded exercise therapy (26%). If diagnosed with CFS, the public would seek information by talking to a family doctor (72%), searching the Internet (54%), and talking to medical specialist (25%). Only 7% would join a support group.

Conclusion:
Our results are consistent with findings that HCP have high awareness and knowledge of CFS, and nearly 80% of HCP classified CFS as a medical or as both medical and psychiatric condition. However, HCP and public view of medical or psychiatric conditions differed. History of CFS diagnosis for HCP may influence this classification. More than 1/3 of HCP had ever diagnosed CFS, which is notable considering the relatively low prevalence of CFS. Study results support development and maintenance of CFS educational materials for the Internet and providing family doctors with tools to engage patients in conversations about CFS.

Corresponding author: Dana J. Brimmer, Ph.D., M.P.H., Behavioral Scientist, McKing and CDC, 1600 Clifton Road, MS-A15, Atlanta, Georgia, 30333, dyv4@cdc.gov. **Disclaimer:** The findings and views in this report are those of the authors and do not necessarily reflect the views of the funding agency.

Profile of the Patient with Chronic Fatigue Syndrome; Experience with a Population-Based Registry

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Objectives:
In Spain, there are no epidemiologic studies analyzing the characteristics of patients diagnosed with chronic fatigue syndrome (CFS) according to the criteria of Fukuda. Thus, the prevalence and incidence of this nosologic condition, which causes considerable disability in personal, social, and work-related activity, is currently unknown. This study determines the sociodemographic, clinical, and therapeutic characteristics of a large series of CFS patients in our setting.

Patients and Method:
All patients who consulted for disabling chronic fatigue and met the diagnostic criteria of Fukuda were included. Patients underwent a diagnostic protocol that included complete laboratory analyses, chest x-ray, abdominal ultrasound, and psychiatric assessment. Sociodemographic data, symptoms, work situation, and treatments prescribed at the time of the diagnosis were recorded. .

Results:
The study included 981 patients with CFS (91 men and 890 women), with a mean age of 47,9 years, 66% were married, 60% carried out specialized work, and 7% were housewives. Among the total, 60% had a secondary school or university education. There was a family background of CFS in 12%, fibromyalgia in 10%, and other immunological diseases in 26.4%. The mean age at the onset of symptoms was 37,5 years and the mean interval from the onset of fatigue to the diagnosis was 116,5 months. The onset was sudden in 20% and gradual in 61%. An evident trigger was documented in 60% (infection, delivery, and a stressful life event). At the time of the diagnosis, 62.5% of patients were not working (sick leave 34% and work disability 37%). The treatment received at diagnosis included medication for the symptoms (analgesic, anxiolytic, and antidepressive agents) in 78,3%, alternative treatments in 3%, and programmed physical exercise and/or cognitive behavioral therapy in 5%.

Conclusions:
When evaluating a patient with incapacitating chronic fatigue, it is essential to identify cases that meet the criteria for CFS. In our setting, this condition predominantly affects middle-aged women who have a secondary or university education and work at specialized jobs. The onset of symptoms often occurs following an identifiable trigger. The condition leads to severe dysfunction in the personal, social, and work-related activities of daily life.

*This study is supported by a research grant (Beca Mutua Madrileña, 2007)

ABSTRACTS

General Session Sunday, September 25, 2011

Session: RESEARCH DEVELOPMENTS IN GENOMICS AND GENETICS

Chair: Christine Kozak, Ph.D.

Expression Patterns of miRNAs in Lymphocytes In Patients with Chronic Fatigue Syndrome

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9. Queensland Health, Gold Coast Population Health Unit, Southport, Gold Coast, Queensland, Australia.

Objective:
MicroRNAs (miRNAs) and transcription factors regulate gene expression and thus are important in modulating the immune responses. Changes in these molecules may be implicated in diseases such as Chronic Fatigue Syndrome (CFS). A number of transcription factors have been shown to be upregulated in CFS patients. However, the role of miRNAs remains to be determined. As cytotoxic activity is decreased in Natural Killer (NK) cells and $CD8^+$T cells, this study assesses the role of miRNAs molecules in $CD8^+$T cells and NK cells in CFS patients.

Methods:
30 CFS patients meeting the CDC case definition (45.3±11.7 yrs) and 30 healthy controls (41.8±9.6 yrs) were recruited into the study. Blood samples were collected from all participants following which lymphocytes were preferentially isolated via a negative isolation system to yield a pure sample of NK and $CD8^+$T cells. RNA was extracted and converted into cDNA and miRNAs of interest were assessed using RT-qPCR. Statistical analysis was performed using the t-test.

Results:
Of the fifteen miRNAs investigated six were found to be down regulated in both the NK and $CD8^+$T cells in CFS patients compared with healthy controls. Most of these miRNAs target genes that are involved in cell cycle regulation, apoptosis and toll like receptor expression.
Conclusion: This study confirms changes in miRNA expression in cytotoxic cells that may be related to the poor function of these cells in CFS patients.

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Pathway-Focused Genetic Evaluation of Immune and Inflammation Related Genes in CFS

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Objectives:
There is evidence that immune and inflammatory alterations are important in CFS. The objective of this study was to determine if genetic variants in inflammation and immune pathways could be linked to CFS as well as to quantitative measures of functional impairment, fatigue and symptom inventory.

Methods:
Participants were identified from a population-based study. This analysis included 362 Caucasian subjects: 121 non-fatigued (NF); 50 CFS with no medical/psychiatric exclusions (CFS); 129 fatigued but insufficient symptoms or fatigue for CFS (ISF) with no medical or psychiatric conditions; and 62 CFS except for medical/psychiatric exclusions (CFS-exclusions). We used a pathway-focused genetic analysis of immune and inflammation related genes with the Affymetrix Immune and Inflammation Chip that covers 11K single nucleotide polymorphisms (SNP) in 1000 genes representing 38 sub-pathways in immune response and inflammation. The manufacturer's protocol was followed for genotyping and accuracy was validated by pyrosequencing. Golden Helix SVS software was used for genetic analysis. SNP functional annotation was done using SPOT and GenomePipe programs.

Results:
Compared to NF controls, CFS was associated with 34 functionally relevant SNPs ($p=2.68 \times 10^{-2}$ – 1.31×10^{-5}). Twelve of these SNPs are in genes playing a role in pathways related to complement cascade (*SERPINA5*, *CFB*, *CFH*, *MASP1* and *C6*), chemokines (*CXCL16*, *CCR4*, *CCL27*), cytokines/cytokine signaling (*IL18*, *IL17B*, *IL2RB*), and Toll-like receptor signaling (*TIRAP*, *IRAK4*). While 11 out of 34 SNPs remained associated with ISF compared to NF, only 4 of the 34 SNPs remained associated with CFS-exclusions. A polymorphism (rs11214105) in the 5'upstream regulatory region of *IL18* was associated with both CFS and ISF (CFS, $p=1.52 \times 10^{-2}$; ISF, $p=2.03 \times 10^{-2}$). In CFS, this SNP associated with MFI subscale of physical fatigue ($p=7.1 \times 10^{-3}$), SF-36 subscale of body pain ($p=9.7 \times 10^{-3}$) and summary

score for CFS case defining symptoms (2.6×10^{-5}). With all these associations, the minor allele increased the risk of the associated phenotype. Similarly, the minor allele of rs7616342 in *KCNH8,* representing the p38/MAPK signaling pathway, increased the risk for CFS ($p=1.31 \times 10^{-5}$), and was also associated with MFI mental fatigue subscale ($p=9.0 \times 10^{-3}$).

Conclusion:
This study identified a number of novel and functionally relevant genetic variants in complement cascade, chemokine and cytokine signaling pathways associated with CFS. Differences in these associations found for subjects with exclusionary conditions otherwise meeting criteria for CFS (CFS-exclusions) suggests important differences between these groups. Further replication and functional studies are needed to support the results of this study.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agency

Gene Expression Of Sensory Ion Channels, Adrenegic Receptors and Cytokines: Potential Biomarkers for CFS and Fibromyalgia

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Objectives:
To determine whether baseline and/or post-exercise expression of genes involved in signaling and modulating sensory fatigue and muscle pain are potential biomarkers for distinguishing patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia Syndrome (FM) from healthy controls.

Methods:
Forty eight Patients with CFS-only or CFS with comorbid FM, 18 Patients with FM that did not meet criteria for CFS, and 49 healthy Controls underwent moderate exercise (25 min at 70% of age-predicted maximum heart rate on Air-Dyne). Blood samples were taken before and 0.5, 8, 24, and 48 hours after exercise. Leukocytes were immediately isolated in buffer, number coded for blind processing, and flash frozen. Using real-time, quantitative PCR, the amount of mRNA for 13 genes (relative to control gene) involved in sensory ion channel, adrenergic, and immune functions was compared between groups at baseline and following exercise. Visual-analogue measures of fatigue and pain were taken before, during, and after exercise, including concurrently with all blood samples. Changes in amounts of mRNA were correlated with these measures, with history of orthostatic intolerance and with blinded ratings of disorder severity by the treating physician derived from multiple clinics.

Results:
No gene expression changes occurred following exercise in Controls except for inconsistent increases in ß-1 adrenergic receptor. In 71% of CFS patients, moderate exercise increased most sensory ion channels and adrenergic receptors and one cytokine gene for 48 hours. These post-exercise increases correlated with numerical ratings of fatigue and pain, and greater increases were shown by patients with higher physician ratings of disorder severity. In contrast, for the other 29% of CFS patients, adrenergic α-2A receptor expression was decreased at all time points after exercise; other genes were not altered. History of orthostatic intolerance was significantly more common in the α-2A decrease subgroup. FM only patients showed no post-exercise alterations in gene expression, but their pre-exercise baseline mRNA for two sensory ion channels and one cytokine were significantly higher than Controls.

Conclusions:
At least two subgroups of CFS patients can be identified by gene expression changes following exercise. The larger subgroup showed increases in mRNA for sensory ion channels and adrenergic receptors and a cytokine. Both self-rated and physician-rated symptom severity was associated with greater post-exercise increases in these genes. The smaller subgroup contained most of the CFS patients with orthostatic intolerance, showed no post-exercise increases in any gene, and was defined by decreases in mRNA for α-2A adrenergic receptor. FM only patients can be identified by baseline increases in 3 genes. Post-exercise increases for 4 genes meet published criteria as an objective biomarker for CFS, and could be useful in guiding treatment selection for different subgroups.

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Gene-Exposure Interactions In The Etiology Of Gulf War Illness: Evidence Of Increased Vulnerability to Neurotoxicants in Identifiable Veteran Subgroups

Lea Steele, Ph.D.

Objectives:
Epidemiologic and clinical studies have implicated wartime exposures to neurotoxicants (pyridostigmine anti-nerve gas pills, pesticides, and low-level nerve agents) as risk factors for Gulf War illness (GWI), but it is unclear why some troops developed GWI after the 1991 Gulf War (GW) while others, with similar experiences and exposures, remained healthy. This study investigated whether genotype or activity of paraoxonase (PON1), a circulating enzyme whose isoforms differentially hydrolyze pesticides and nerve agents, is associated with variable risk for GWI in veterans of the 1991 Gulf War.

Methods:
Case-control study of a population-based sample of 91 veterans who served in the Army as enlisted personnel during the 1991 Gulf War: 49 Gulf War veterans with GWI, 19 GW veteran controls, and 23 nondeployed veteran controls. Veterans provided information on wartime experiences and exposures, and blood samples for determining PON1 genotype at position 192, and PON1 activity in three substrates: paraoxon, phenyl acetate, and diazoxon. In addition to general case-control comparisons, exploratory analyses evaluated interactions between genotype and exposures in the risk for GWI.

Results:
Overall, a somewhat higher proportion of GW cases (22%) than GW controls (6%) were PON1192 RR homozygotes ($p=0.09$). PON1 activity in paraoxon was significantly lower in GW controls than in GWI cases ($p=0.04$) and nondeployed controls ($p=0.05$), with no significant differences noted in other substrates. In exploratory evaluation of GWI risk in PON1192 genetic subgroups, QQ homozygotes were at significantly increased risk for GWI if they reported wearing pesticide-treated uniforms (OR = 21.0, exact $p<0.01$) or prolonged use of pyridostigmine bromide (OR=11.2, exact $p<0.01$), although these exposures were not associated with GWI in veterans with QR and RR genotypes. Among veterans with QR and RR genotypes, the only significant GWI risk factor was hearing chemical alarms in theater (OR=7.6, exact $p=0.04$), while hearing alarms was not a risk factor for QQ homozygotes (OR= 0.75, exact $p=0.34$).

Conclusions:
Findings support earlier indicators that GWI may be associated with PON1 genotype and activity levels, with GW PON1192RR homozygotes at somewhat increased risk for GWI overall. Detailed investigations from our small sample provided significant results in support of the following hypotheses: 1) GW veterans whose PON1 genotype (QQ) is known to provide slower hydrolysis of some organophosphate pesticides were at increased risk for GWI in relation to reported use of pesticides and prolonged use of pyridostigmine bromide during deployment, and 2) GW veterans who carry the R allele at PON1192, which is known to provide inefficient hydrolysis of sarin, were at increased GWI risk if they heard chemical alarms in theater. These preliminary findings identify significant gene-exposure interactions in the directions expected for substrates preferentially hydrolyzed by PON1192 Q and R isozymes, and warrant further evaluation in a larger sample.

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Comparing Gene Expression Patterns in CFS and GWI Using the Kerr ME/CFS Platform

Lina Garcia, M.D.
Jonathan Kerr, MD^, Mary Ann Fletcher, PhD*, Connie Sol, MA*, and Nancy Klimas, MD** *University of Mimi Miller School of Medicine, , ^St George's University of London, United Kingdom,**corresponding author nklimas@miami.edu, University of Miami Miller School of Medicine and Miami VA Medical Center

There have been a number of studies utilizing genomics to better understand and define CFS/ME. Jonathan Kerr's group published a series of studies that defined 79 genes associated with this illness, then used the same method to develop biologically defined subgroups (1). The Miami group has been studying both GWI and CFS/ME using gene activation patterns and proteomics, before during and after an exercise challenge to better understand the mediators of persistence and relapse. In this study we collaborated with Dr Kerr, comparing CFS/ME (n=25), control (n=53) and GWI samples (n=25), the GWI samples studied were drawn prior to the exercise challenge.

The data from the CFS/ME cohort confirmed the findings from Dr. Kerr's earlier studies. There were significant differences when compared to controls in expression of genes that regulate intracellular pathways mitochondrial function, cell wall and signaling pathways. Genes which regulate cytokine regulation were also significantly different than controls, particularly the pro-inflammatory cytokines TNFa and IL6; antiviral pathways Interferon alpha, beta and omega, and the anti-inflammatory cytokine IL10.

When compared to Gulf War Illness there are some important overlaps:

EB12, an EBV induction gene is 6 fold higher than controls in CFS/ME, 2 fold higher in GWI, both significant differences ($p<.005$) ETS1, a viral oncogene was also upregulated in both groups. ($p<.-0005$) Transcription factor 3, which regulates immunoglobulin production, was markedly elevated in GWI, less so though significantly elevated in CFS/ME. ($p<.005$) Apoptosis genes were markedly upregulated in both groups though GWI saw elevations were 400 fold higher than CFS/ME. ($p<.0005$).

However, the overall trend was that most of the gene regulation abnormalities that are associated with CFS in the Kerr platform were not significantly different in GWI than in controls , and often moved in the opposite direction down regulating intracellular processes in GWI that were upregulated in CFS (73 of 87 genes studied). Using a comprehensive platform, additional genes specific for GWI have been identified by the Miami group (presented separately).

1. Kerr JR, et al. 2008. Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis. J Infect Dis 197(8):1171-84.

Session: ADVANCES IN BRAIN AND NEUROENDOCRINE FUNCTIONING

Chair: Andrew H. Miller, M.D.

Regional Grey and White Matter Volumetric Changes in Chronic Fatigue Syndrome (Myalgic Encephalomyelitis): A Voxel-Based Morphometry 3T MRI Study

I. H. Treasaden, M.B., B.S., LRCP, MRCS, FRCPsych, LLM
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Objectives:
It is not established whether or not myalgic encephalomyelitis/chronic fatigue syndrome (CFS) is associated with structural brain changes. The aim of this study was to investigate this by conducting the largest voxel-based morphometry study to date in CFS.

Methods:
High-resolution structural 3-T cerebral MRI scanning was carried out in 26 CFS patients and 26 age- and gender-matched healthy volunteers. Voxel-wise generalized linear modeling was applied to the processed MR data using permutation-based non-parametric testing, forming clusters at $t > 2.3$ and testing clusters for significance at $p < 0.05$, corrected for multiple comparisons across space.

Results:
Significant voxels ($p < 0.05$, corrected for multiple comparisons), depicting reduced grey matter volume in the CFS group, were noted in the occipital lobes (right and left occipital poles; left lateral occipital cortex, superior division; and left supracalcrine cortex); the right angular gyrus; and the posterior division of the left parahippocampal gyrus. Significant voxels ($p < 0.05$, corrected for multiple comparisons), depicting reduced white matter volume in the CFS group, were also noted in the left occipital lobe.

Conclusion:
These data support the hypothesis that significant neuroanatomical changes occur in CFS, and are consistent with the complaint of impaired memory that is common in this illness; they also suggest that subtle abnormalities in visual processing, and discrepancies between intended actions and consequent movements, may occur in CFS.

Dr. Ian H. Treasaden, M.B., B.S., MRCS, LRCP, FRCPsych, LL.M., Consultant Psychiatrist and Honorary Clinical Senior Lecturer, West London MHT and Imperial College London; Head of Forensic Neuroscience, Department of Imaging, Imperial College, UK.
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Evidence For Reduced Aldosterone in Persons with Chronic Fatigue Syndrome

Roumiana S. Boneva, M.D., Ph.D.
James F. Jones, Elizabeth R. Unger
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Objectives:
Aldosterone, a mineralocorticoid hormone of the adrenal gland, controls the absorption of salt and water in the kidneys and the intestine and thus the overall blood volume. Mineralocorticoid receptors in the brain are involved in regulation of blood volume and sympathetic outflow regulation. A few studies have suggested lower blood volume and lower heart stroke volume in persons with chronic fatigue syndrome (CFS) and some persons with CFS experience postural hypotension. Because altered cortisol secretion has been found in a number of CFS studies, adrenal dysfunction has been suggested. Surprisingly, only one prior study examined aldosterone in CFS, finding lower aldosterone in CFS compared to controls. The current study was performed to explore the hypothesis that aldosterone levels in persons with CFS may differ from those in controls of similar age, sex, and race.

Methods:
Participants were identified from a population-based study including 70 CFS cases who met the international 1994 CFS case definition and 212 controls of similar age and race. A morning blood sample, collected after participants rested 30 minutes in supine position, was used to test for serum aldosterone. Testing was performed at Quest Diagnostics using liquid chromatography tandem mass spectrometry (analytical sensitivity 1 ng/dL). The Wilcoxon nonparametric test was used for comparison of non-normally distributed numeric variables (aldosterone). Chi square test and logistic regression were used to assess magnitude of associations; for these tests aldosterone was dichotomized at its median value 4 ng/dL in controls, which also equaled the lowest normal lab reference value.

Results:
Cases and controls did not differ significantly in mean age (47.8 and 47.7, respectively) or race distribution (78.3% and 80.7% Whites, respectively). The CFS group had a higher proportion of women (91.3% vs 67.5%) and a higher mean body mass index than the control group (BMI, 28.9 vs 26.9), $p<0.005$ for both. The CFS group had lower aldosterone levels compared to controls (mean 4.46, median 3, range 1 to 19 ng/dL vs mean 6.05, median 4, range 1to 76 ng/dL, respectively), $p<0.0001$ (Wilcoxon non-parametric test). Persons with CFS were 65% more likely to have aldosterone level of <4 ng/dL, OR=1.65 (95% CI, 0.95-2.85), p=0.07. The OR changed slightly after adjusting for BMI, OR=1.58 (0.93-2.74), p=0.11, but minimally after adjusting for sex, OR= 1.69 (95% CI, 0.96- 2.97), p=0.07. A limitation of the study is that aldosterone was measured only in supine position (less sensitive for identifying alterations in aldosterone secretion) and information on dietary salt intake was not available.

Conclusions:
These results support a previous study's finding of relatively lower aldosterone levels in CFS subjects compared to controls. Further studies of aldosterone in CFS should measure its response to challenge such as salt restriction and changes in aldosterone levels from recumbent to upright position.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agency

Interaction of Self-And Illness-Related Cognitive Processing In The Right Anterior Insula of CFS Patients: An fMRI Study

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Objectives:
Based on the core clinical complaints of CFS patients several groups have suggested that CFS symptoms may be at least partially linked to altered cognitive or pre-cognitive processing in the central nervous system. Targeting the identification of the neural substrates of alterations of internal body signals and self-related information seems warranted. This study investigates brain responses to self- and illness-related semantic information in a sample of CFS patients compared to matched control subjects, using functional magnetic resonance imaging (fMRI). We focus on the right anterior insula (rAIC), for its purported role in interoceptive processing and awareness (Craig 2002, 2009, Nat Rev Neurosci), and on the interaction of the self-related and illness-related semantic processing.

Methods:
Twenty-one subjects meeting the 1994 International criteria for CFS, and 42 non-fatigued (NF) subjects performed a semantic processing task while undergoing an fMRI scan. The stimuli consisted of visually presented short sentences requiring the participants to provide a "true" or "false" answer. The semantic content was arranged according to a 2 x 2 x 2 factorial design, where the three factors were (a) Self-related: yes/no, (b) Illness-related: yes/no, and (c) Valence: negative/positive. We assessed the effect of processing Self-related versus Non self-related semantic information, across the two groups of CFS and NF subjects in a single acquisition run of functional images by examining a set of regions of interest.

Results:
In both CFS and NF subjects: 1) the insular response to self-related sentences tended to decrease compared to response to non self-related sentences, in both CFS and NF subjects; 2) the insular response to non-self sentences did not differ with respect to illness-related material or not; 3) the insular response to self-related/illness-related sentences was greater than that for self-related/non illness-related only in CFS subjects. A qualitatively similar pattern was observed for the response time data. The statistical significance for the group difference in the interaction effect (3-way ANOVA: Group x Self-related x Illness-related) was p=0.0034 for the rAIC activation data and p=0.0022 for the reaction time data.

Conclusions:
Self is a multifaceted construct that relies in part on interoception (monitoring of internal physiology and consequences of external stimuli) via the anterior insular cortex through recognition of subjective feelings (Craig). The changes observed here in CFS subjects indicate responses to an increased mental load or to a cognitive conflict within the semantic dimensions of self and illness. This is evidence that (1) there is a real alteration of body physiology underlying the CFS symptoms, and the observed altered rAIC response reflects the (normal) cognitive and pre-cognitive acquisition of an abnormal physiological landscape in the body; or (2) the actual interoceptive landscape is acquired cognitively and pre-cognitively in an altered way in CFS subjects, enhancing the prominence of normal bodily signals related to fatigue.

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Disclaimer: The findings and views in this report are those of the authors and do not necessarily reflect the views of the funding agency.

Decreased Basal Ganglia Activation in CFS Subjects is Associated With Increased Fatigue

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Objectives:
Altered basal ganglia function has been associated with fatigue in a number of neurologic disorders, as well as in patients exposed to chronic immune stimulation. Patients with chronic fatigue syndrome (CFS) have been shown to exhibit symptoms suggestive of decreased basal ganglia function as reflected by psychomotor slowing on neurocognitive testing, which in turn correlated with fatigue. In addition, CFS patients have been found to have increased markers of immune activation. In order to directly test the hypothesis of decreased basal ganglia function in CFS, we conducted a functional magnetic resonance (fMRI) study on a sample of CFS patients and matched controls, using a reward-processing experimental protocol.

Methods:
A community-derived sample of 59 male and female subjects, including 18 patients diagnosed with CFS according to 1994 CDC criteria and 41 non-fatigued healthy controls, participated in the study. All subjects were free of psychotropic medications as well as significant depressive symptoms, as determined by a Zung Depression score <60. Groups were similar in age, sex, and race. While undergoing fMRI scanning, subjects performed a monetary gambling task previously shown to strongly activate basal ganglia in the win versus lose condition. To focus our analysis on the specific basal ganglia regions activated by the task, the following procedure was employed: (1) a whole-brain group analysis revealing the general activation pattern for the win-lose contrast across all subjects was performed; (2) the resultant statistical parametric brain map thresholded at $p<0.05$, corrected for multiple comparisons, was intersected with a set of basal ganglia regions of interest (ROIs: caudate nucleus, putamen, and globus pallidus), obtained from a probabilistic cytoarchitectonic brain atlas included in the SPM
Anatomy Toolbox; (3) for each subject, the average value of win-lose activation contrast in each ROI was extracted for group comparisons and correlational analyses.

Results:
Compared to non-fatigued controls, patients with CFS exhibited significantly decreased activation in the right caudate ($p=0.01$) and right globus pallidus ($p=0.02$). Decreased activation in the right globus pallidus was significantly correlated with increased mental fatigue ($r2=0.49$, $p=0.001$), general fatigue ($r2=0.34$, $p=0.01$) and reduced activity ($r2=0.29$, $p=0.02$), as measured by the Multidimensional Fatigue Inventory. No such relationships were found in control subjects.

Conclusions:
These data suggest that reduced basal ganglia activation may contribute to symptoms of fatigue in CFS subjects. Given the central role of dopamine in basal ganglia regulation, these data also indicate that alterations in dopamine metabolism may be involved. Further understanding of potential alterations of dopamine transmission and metabolism in basal ganglia, due to activated immune pathways or other causes, may lead to new pharmacologic strategies targeting dopamine and the basal ganglia for the treatment of CFS symptoms.

The findings and views in this report are those of the authors and do not necessarily reflect the views of the funding agency.

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Assessment of Regional Cerebral Blood Flow in CFS Using Arterial Spin Labeling MRI

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Objectives:
Chronic Fatigue Syndrome (CFS) is an unexplained illness characterized by debilitating fatigue that is not ameliorated by sleep[1,2]. In two previous independent samples of CFS, we found increased ventricular lactate, which we had postulated to be due to oxidative stress, a secondary mitochondrial dysfunction and/or decreased regional cerebral blood flow (rCBF). To investigate the latter possibility, we used arterial spin labeling MRI[3] to compare rCBF in patients with CFS, and in age-and sex-matched patients with major depressive disorder (MDD) and healthy volunteers (HV).

Methods:
Fourteen CFS [31.9±8.6 yrs, 3M/11F], 13 MDD [31.4±9.9 yrs, 5M/8F] and 13 HV [27.6±7.4 yrs, 6M/7F] subjects were recruited for this study. The two patient groups were psychotropic medication-free for at least 1 week prior to scanning. rCBF was measured in each participant using ASL on a 3.0T GE MRI system. The resulting rCBF images were reconstructed on-line and normalized to the Montreal Neurological Institute (MNI) PET template. Groupwise voxel-based analysis of the ASL data was performed using SPM version 5, followed by between-group ANCOVA comparisons in which age and gender were covariates.

Results:
Significantly decreased rCBF values were found in the left anterior cingulate cortex (ACC) [p=0.039] and the right lingual region [p=0.016] in CFS compared to HV, while a trend toward significantly lower rCBF was found in the left ACC region in MDD subjects compared to HV [p = 0.08]. rCBF values for CFS and MDD did not differ significantly [p>0.05].

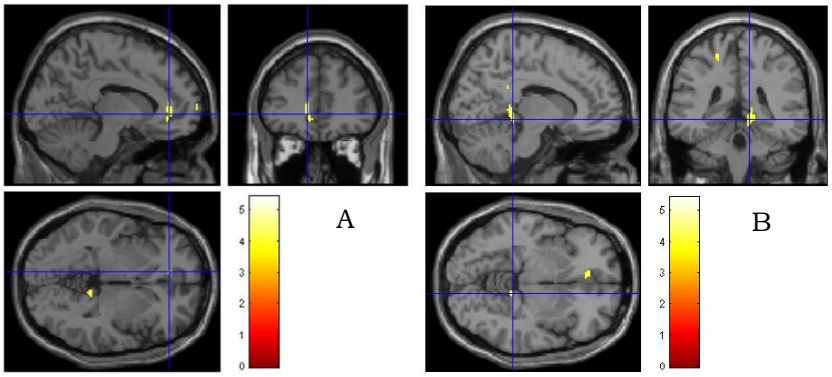

Figure 1: Maps showing statistical significance of regions of reduced cerebral blood flow in CFS subjects versus healthy controls are shown. A) Left anterior cingulate cortex [p=.039], B) right lingual Region [p=0.016].

Conclusion:
The present finding of decreased rCBF in CFS is consistent with prior measurements using ^{111}Xe-CT[4] or ASL[5], although less pervasive and more spatially focused, which might be due to methodological differences. Our observation of a trend toward hypoperfusion in the ACC in MDD, a region where we had previously reported finding amino acid neurotransmitter abnormalities[6], provides further evidence for the involvement of this brain structure in the disorder. Due to the relatively limited spatial extent of the rCBF decrease in CFS, it is unclear whether the resulting hypoperfusion would account for our previous observation of elevated ventricular lactate in the disorder. However, it should be noted that the rCBF values in individual voxels throughout the brain were largest in HV and lowest in CFS, which could cumulatively lead to global hypoperfusion and to lactate increases. Larger studies in well-characterized subjects are warranted to confirm this possibility, as well as the overall results of this pilot study.
[1] Mathew et al, NMR Biomed 2009; 22:251. [2] Murrough JW et al, NMR Biomed 2010; 23:463. [3] Detre JA, Alsop DC, Eur J Radiol 1999; 30:115. [4] Yoshiuchi K et al, Clin Physiol Funct Imag 2006; 26:83. [5] Biswal B et al, J Neurol Sci. 2011; 301:9-11. [6] Price RB et al. Biol Psychiatry 2009;65:792..

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Session: IACFS/ME CLINICAL PRACTICE MANUAL: DEVELOPING A NEW PRIMER

Guidelines Panel
Fred Friedberg, Ph.D., Rosemary Underhill, M.D., Rosamund Vallings, MNZM, MB BS, Alan Gurwitt, M.D.
Leonard A. Jason, Ph.D., Lucinda Bateman, M.D., Kenneth Friedman, Ph.D.

The IACFS/ME primer committee is writing a practice manual intended to inform the larger primary practitioner community about the basics of good clinical care of patients with CFS/ME. This session will present an overview of our efforts to date. We will also focus on selected topics where we invite your feedback about issues such as: non-pharmacological interventions vs. medications, the case for evidence-based clinical care, and effective dissemination of the completed primer.

SUMMARY OF THE CONFERENCE

Anthony L. Komaroff, M.D.
No Abstract Submitted-This presentation is based on all lectures presented over the previous days which does not allow for an abstract to be published.

POSTER PRESENTATION ABSTRACTS

VIROLOGY

Systemic Immune Activation in XMRV Positive CFS/ME Patients

Kenny De Meirleir
Marc Frémont, Kristin Metzger, Chris Roelant
Vrije Universiteit Brussel, Belgium

Objectives:
Chronic activation of the immune system is present in progressive HIV infection and is a better predictor of disease outcome than plasma viral load. Several studies suggest that XMRV is involved in the pathophysiology of CFS/ME. We wanted to test the hypothesis that the systemic immune activation in XMRV positive CFS patients is similar to the one observed in HIV.

Methods:
Sixteen CFS patients fulfilling the Canadian criteria for CFS and were found positive for XMRV by co-culture technique were included in the study. Reference data were used from a large cohort of healthy individuals.
Complete immunophenotyping was performed on venous blood and also elastase activity, C4a, IgG3, cytokines, sCD14, perforin were measured. Stool IgA was also determined.
Statistical analysis was performed independently from our group by Professor D. Coomans (Vrije Universiteit Brussel / James Cook University).

Results:
The number of CD3+ and CD57+ lymphocytes was significantly lower compared to the reference values. C4a and elastase were significantly higher in the XMRV positive CFS population.
Soluble CD14 (which codes for LPS in plasma) was significantly higher at $p < 0.001$ as compared to the reference population. The cytokine panel showed increased IL-10, MCP-1, MIP-1 beta and IL-8 serum levels. Other lymphocyte subsets showed no difference from the reference in the XMRV positive patients.
Stool IgA and IgG3 were statistically lower in the XMRV positive patients.

Discussion:
The results of this study show that XMRV positive patients have lymphocyte numbers and CD57+ lymphocytes below normal as is observed in HIV.
XMRV positive CFS patients have an activated innate immune system (elastase activity and C4a are increased) which could be related to microbial translocation as their sCD14 is significantly higher than expected; sCD14 strongly correlates with plasma LPS.
Low stool IgA also indicates dysfunctional mucosa-associated lymphomal tissue (MALT) in XMRV positive CFS patients. Furthermore their IgG3 serum levels are lower than in the controls.
Serum levels of the cytokines IL-8, IL-10, MCP-1 and MIP-1beta are increased in the patients and might constitute a biological signature for the viral infection.
These observations and other unpublished data on serum LPS in CFS patients, provide evidence for microbial translocation being part of the pathophysiology of XMRV positive CFS patients.

Presence of Active HHV-6, HHV-7 and Parvovirus B19 Infection/Co-Infection In Patients With Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

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Introduction:
CFS/ME is a chronic neuro-immune illness defined by combination of non-specific symptoms of uncertain cause and pathogenesis. Immunomodulating viruses (HHV-6, HHV-7, parvovirus B19) are considered as possible trigger factors for CFS/ME development. The aim of this study was to evaluate frequency of HHV-6, HHV-7 and B19 infection activation/co-activation and association with clinical findings in CFS/ME patients.

Methods:
108 patients (71 females and 37 males, mean age 37 years) with clinically diagnosed CFS/ME corresponding to CDC definition criteria were enrolled in the study. Plasma/serum samples were tested for HHV-6 and B19 IgG and IgM antibodies using ELISA. Qualitative and quantitative PCRs were used for viral genomic sequences detection in PBL and cell-free plasma DNA samples.

Results:
HHV-6 specific IgG and IgM antibodies were detected in 81.5% and 14.8% patients, respectively, B19 specific IgG and IgM antibodies - in 73.1% and 26.9% patients, respectively. Virus specific sequences were detected in 70/108 (64.8%) patients plasma DNA samples, from them single virus sequence - in 41 (38.0%) DNA samples (HHV-6 - 2, HHV-7 - 28, B19 - 11) and double or triple virus sequences -

in 29 (27.0%) samples (HHV-6+HHV-7 - 10, HHV-7+B19 - 15, HHV-6+HHV-7+B19 - 4). HHV-6-PBL load was higher in patients with active HHV-6 and HHV-7 co-infection then in patients with single HHV-6 infection ($1007.8\pm367.1x10^3$, $133.0\pm10.3x10^3$, copies/μg DNA, respectively). Severe chronic fatigue for at least six months or longer was recognized in all patients independently from the causation of the active infection. Subfebrility, tender cervical or axillary lymph nodes and post-exertional malaise were not revealed in patients with single B19 infection but were detected in patients with single HHV-7 infection (50.0%, 75.0%, 100%, respectively) and HHV-6+HHV-7 co-infection (68.9%, 83.4%, 88.9%, respectively). Persistent muscle and muscular weakness were detected in all patients with manifestation more severe in patients with HHV-6, HHV-7 and HHV-6+HHV-7 infection. Multi-joint pain also was determined in all patients with stronger symptoms in HHV-7+B19 (82.5%) and HHV-6+HHV-7+B19 (100%) co-infection cases. Neuropsychological disturbances were detected in all patients: impaired memory – in 85.0% patients with active HHV-7 and HHV-6+HHV-7 infection, and impaired concentration – in all patients with active B19, HHV-7+B19 and HHV-6+HHV-7+B19 infection. Unrefreshing sleep was revealed in all patients with sleepiness more characteristic in patients with HHV-7, HHV-6+HHV-7 (87.5%) and HHV-6+HHV-7+B19 infection, and sleepless – in all patients with HHV-6, B19 and HHV-7+B19 infection. Headaches of new type were reported from all patients with B19 infection versus 41.7% in patients with HHV-7 and HHV-6+HHV-7 infection.

Conclusion:
High rate of active HHV-6, HHV-7, B19 infection or in combination suggest that each from these immunomodulating pathogens could be trigger factor for CFS/ME development. The association between high frequency of active co-infection and distinctive types of clinical symptoms show necessity of simultaneous study of these viral infections to define possible subsets of CFS/ME.

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Epstein-Barr Virus Latent Abortive Reactivation Replication of the Encoded Gene Products Deoxyuridine Triphosphate (dUTPase) and Deoxyribonucleotide polymerase (DNA polymerase) in Myalgia Encephalomyelitis Chronic Fatigue Syndrome (ME/CFS)

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Methods:
With a specific ME/CFS diagnostic panel, 6 patients with Epstein-Barr Virus (EBV) subset were treated with valacyclovir (14.3 mg/Kg q 6 h) for greater than or equal to 12 consecutive months. EBV assays were repeated every 6-12 weeks in each patient. ELISA assays included EBV, Early Antigen (Diffuse) EBV EA(D), Viral Capsid Antigen (VCA) IgM. Neutralization assays included EBV dUTPase and EBV/DNA polymerase.

Results:

a) EBV VCA, IgM: 51 separate sera were tested for EBV VCA IgM. All were negative.

b) EBV EA(D): 48 separate sera were tested for EBV EA(D). 46 of 48 assays (95.8%) were positive

c) EBV dUTPase: three of 9 (33.3%) positive assays; patient one: five of 7 (71.4%) positive assays; patient two: three of 10 (30%) positive assays; patient three: eight of 10 (80%) positive assays; patient four: three of 8 (37.5%) positive assays; patient five: two of 7 (28.6%) positive assays. Therefore, all 6 patients had positive assays for elevated antibody titers to dUTPase

d) EBV/DNA polymerase: Eight of 10 (80%) patient one: four of 7 (57.1%) patient two: seven of 10 (70%) patient three: nine of 10 (90%) patient four: seven of 8 (88%) patient five:six of 7 (71.4%) were positive assays for EBV DNA polymerase. Therefore, all 6 patients had positive assays fpr elevated antibody titers to EBV DNA polymerase.

Conclusions:
There was no evidence of EBV lytic replication in these ME/CFS patients. There were 47/50 (94%) EBV EA(D) positive assays, 24/51 (47%) dUTPase positive assays, and the 41/52 (78.8%) DNA polymerase positive assays. These data document EBV latent abortive reactive replication in these six ME/CFS patients and suggest a possible etiologic relationship to the ME/CFS.

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Pathogenesis of Chronic Enterovirus Infection in Myalgic Encephalomyelitis (ME/CFS) –in vitro and in vivo Studies of Infected Stomach Tissues

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Objectives:
Chronic enterovirus infection has been implicated in the pathogenesis of ME/CFS. Previously, we demonstrated enteroviral protein (VP1), RNA and non-cytopathic viruses from the stomach biopsies of ME/CFS patients. The basis of viral persistence has not been clearly defined. Enterovirus can form double-stranded RNA (dsRNA) in tissue cultures and in muscles of infected mice and human. We evaluated the presence of dsRNA in the stomach biopsies and possible infectivity of stomach tissues in SCID mice.

Method:
Archived, paraffin-embedded stomach biopsies from CFS patients and controls were stained for dsRNA using anti-dsRNA monoclonal antibody and immunoperoxidase technique. 9 cryopreserved ,VP1+ and dsRNA+ stomach biopsy samples were injected ip into SCID mice; and 2 boiled RNA+ samples, 4 VP1-neg and dsRNA-neg samples and one sample of culture medium were injected ip into other 7 SCID mice as controls. Mice were sacrificed 3-4 weeks after infection, and organs processed for viral cultures, EV RNA and viral protein staining.

Results:
108/132 (82%) and 84/132 (64%) of the stomach biopsies from ME/CFS patients stained positive for VP1 and dsRNA respectively, whereas 4/40 (10%) of the control specimens were positive for dsRNA ($p<0.01$, x^2 test). Pre-treatment with RNase III of selective samples diminished or abolished the dsRNA staining; higher concentrations of enzyme and incubation period were required for specimens from sicker patients. 21/23 (91%) of stomach biopsies previously tested positive for EV RNA by RT-PCR or had grown non-cytopathic virus were positive for dsRNA. Of organs taken from SCID mice injected with stomach biopsies, 7/9 (78%) spleen specimens were positive whereas 0/7 controls were positive for VP1 protein by immunoperoxidase staining ($p<0.01$, x^2 test). 4/9 lung specimens 0/8 of heart, liver and kidney sections demonstrated VP1 staining. All tissue homogenates were negative for EV RNA or growth of virus in BGMK-DAF and WI-38 cells.
Conclusion: DsRNA was frequently demonstrated in the VP 1+ stomach biopsies taken from ME/CFS patients, and most EV RNA+ samples had detectable dsRNA. In pilot experiments, dsRNA+ samples were infectious in SCID mice, as compared to control samples. Enteroviral dsRNA may play a central role in the pathogenesis of chronic EV infection and ME/CFS, and the mechanism should be further investigated.

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PHARMACOLOGIC TREATMENT ADVANCES

Compassionate Use of GcMAF IN ME/CFS Patients

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Objectives:
Immune dysregulation is an established feature of ME/CFS, reflected in the altered balance of immune activity, allowing reduced protection from certain infections, viral re-activation, excess Th2/Th17 activity causing increased inflammatory symptoms and autoimmunity. This is the foundation for symptom expression as well as additional consequences of reduced immune protection (intracellular infection, fungal overgrowth, parasitic infestation, mould sensitivity). Recently t he detection of gamma Retroviral (GRV) Infection involving Murine Leukaemic Virus (MLV) and Xenotropic Murine Retrovirus (XMRV) is shown in a majority ME/CFS and in 3-5% controls (Lombardi et al.). The resultant multisystem illness opens the door to a variety of treatment protocols, but despite this approach, the treatment response is slow, may plateau or not occur.
GcMAF has been shown to enhance immune activity and has been used in the role of cancer therapy and in HIV. Its use in addressing the immune dysregulation in ME/CFS and complications has recently started (on compassionate grounds) in those in whom there is no significant response to other therapies, and who suffer marked limitation due to this illness.

Methods:
Patients (age 18-65) were selected in whom a diagnosis of ME/CFS was made, based upon history, physical examination, routine and specific investigations, and the fulfilment of the Canadian Clinical Criteria and who were diagnosed with XMRV and/or MLV. These included immune and viral studies. They were all XMRV and/or MLV positive.In those patients in whom there was serious illness, were refractory to other treatment protocols and marked limitation due to symptoms severity were administered GcMAF.
It was used in a concentration of 100 nanograms/ml of physiological serum and administered by weekly injections of 0.25 ml to 1.0 ml by intravenous route or subcutaneously.
There was regular follow-up throughout the treatment with review of symptom expression and investigations were performed to monitor treatment response.
Duration of Treatment was for 5-40 weeks

Table 1

ME/CFS Patients (Aged 18-65 years) n=108	
MLV +	34
XMRV co-culture +	54
XMRV Serology +	20

The effectiveness of treatment was assessed by symptom change and expression; monitoring of the condition by routine investigations; measurement of immune response (nagalase, CD57, Perforin, C4A, and comparison with other individual immune parameters shown to be abnormal at the initiation of therapy).

Results:
Table 2: Preliminary data on the outcome: 68/108 (63%) report noticeable improvement.

Percentage of Patients With a Noticeable Improvement of Symptoms n = 68		
Symptoms	**# of patients**	**Percentage**
Fatigue diminished or absent →	44/68	65%
Sleep quality better →	39/68	57%
Pain diminished or absent →	35/68	51%
Neurocognitive function better →	27/68	40%
Recovery faster / less "payback" →	42/68	62%
Orthostatic intolerance* diminished or absent →	22/68	32%*
Digestive problems diminished or absent →	36/68	53%

*Not all patients reported these symptoms prior to initiation of treatment.
Side effects were present in 18 %; these mainly, were but not restricted to headaches and sleep disturbances. This was managed by lowering the dose, which usually solved the problem. Therapy was ceased in 7 % because of severe headaches and/or sleep disturbances.
Delay in response may be attributed to VDR genotype and so effect of therapy may yet to be expressed amongst those regarded at this stage as non-responders.

Conclusion:
The use of GCMAF in XMRV+ and/or MLV+ patients ME/CFS patients for whom other treatments were refractory, has been shown to safely produce symptomatic relief when administered weekly for specific periods of time.
These "positive" preliminary data need to be confirmed in a double-blind placebo controlled GcMAF study.

Vasoactive Intestinal Polypeptide (VIP) Lowers C4a and TGF beta-1, Corrects Refractory Symptoms and Normalizes Abnormal Biomarkers in Patients with CFS

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Background:
CFS patients invariably have low levels of vasoactive intestinal polypeptide (VIP). In two case series of patients meeting the case definition for adult CFS (N=1682), deficiency of VIP occurred in 98% of patients. Less than 10% of controls were VIP deficient. VIP raises cAMP; lowers pulmonary artery (PASP) responses to exercise, blocks peripheral innate immune activation; reduces apoptosis of glial cells undergoing oxidative stress; raises VEGF; restores circadian rhythm; regulates response to olfactory stimuli in the suprachiasmatic nucleus; regulates dendritic calls; regulates Th17 function in autoimmunity; enhances IL-10 production; and modulates innate immunity. In a pilot study in 2010, use of VIP was shown to be safe in human volunteers, providing (1) marked reduction in symptoms and (2) blunted accentuated pulmonary artery response to exercise. We studied the clinical responses in 100 consecutive CFS patients with refractory illness to intranasally administered VIP.

Methods:
After informed consent, patients with symptoms meeting the Fukuda definition of CFS were treated with 50 mcg of VIP given four times a day via nasal aerosol for two months. There were no dropouts in the study. Pre- and post-VIP measures included symptoms; visual contrast sensitivity (VCS); levels of VIP, VEGF, MSH, C4a, TGF beta-1, MMP9, testosterone, estradiol, lipase, vitamin D 25-OH, CBC and CMP. Exclusion criteria included three indicators known to be associated with reduced benefit (1) depressed visual contrast sensitivity; (2) ERMI > 2; (3) presence of multiply antibiotic resistant biofilm-forming coagulase negative staphylococci in deep nasal aerobic spaces.

Results:
Patients tolerated the drug well. Symptom reduction occurred in all patients with normalization of mean VEGF, MMP9, C4a and TGF beta-1. Testosterone rose and estradiol fell in males with no changes in females. No adverse effects on CBC and CMP were noted. Abnormal vitamin D 25-OH normalized. One person developed an elevated level of lipase without abdominal pain.

Discussion:
Treatment with VIP provided restored clinical functioning in a cohort of patients with severe CFS illness. As a regulatory neuropeptide, VIP has multiple salutary effects on human physiology. Replenishment of deficiency states returns quality of life and stabilizes inflammatory responses.

Conclusions:
Evaluation of clinical use of VIP will require additional clinical trials but early results show safety and marked benefit in severely affected CFS patients.

NON-PHARMACOLOGIC TREATMENT ADVANCES

Resveratrol Improves Hippocampal Atrophy in Mice with Chronic Fatigue

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Abstract:
Neuroimaging evidence showed structural and/or functional abnormalities existing in the central nervous system, especially the hippocampus, in chronic fatigue syndrome (CFS) patients. However, its pathophysiologic mechanisms are unclear in part due to the lack of an applicable animal model. We established a chronic fatigue murine model by six repeated injections of *Brucella abortus* antigen to mice, which was manifested as reduced daily running activity and hippocampal atrophy. Thereafter, resveratrol, a polyphenolic activator of sirtuin 1, was used for treatment in this model. Daily running activity was increased by more than 20%, and the hippocampus was enlarged after 4-week resveratrol therapy. Furthermore, resveratrol inhibited neuronal apoptosis and expression of hippocampal acetylated p53 in the fatigue mice. Resveratrol also improved neurogenesis and expression of brain-derived neurotrophic factor mRNA in the hippocamous. We concluded that repeated injection of *B. abortus* antigen could induce hypoactivity and hippocampal atrophy in mice. Resveratrol may be effective for improving fatigue symptoms and enlarging the atrophic hippocampus by repressing apoptosis and promoting neurogenesis.

Objectives:
Neuroimaging indicates that structural and/or functional abnormalities exist in the central nervous system, especially in the hippocampus of patients with chronic fatigue syndrome (CFS). However, the pathophysiological mechanisms of CFS are still unclear, which is partly because of the lack of a suitable animal model.

Methods:
In the present study, we established a mouse model of chronic fatigue by six repeated injections of *Brucella abortus* antigen into Balb/c mice.

Results:
Which was manifested as a significant reduction in daily spontaneous running activity, and hippocampal atrophy.Thereafter, resveratrol (RSV), a polyphenolic activator of sirtuin 1 (Sirt1) was used for the treatment of this model.
The daily spontaneous running activity was increased by more than 20%, and the hippocampus was enlarged after 4 weeks RSV therapy. Furthermore, RSV inhibited neuronal apoptosis and the expression of hippocampal acetylated-p53 in the chronic fatigue mice model, which may have contributed to the upregulated deacetylation of p53 by Sirt1. In addition, RSV improved neurogenesis and expression of brain-derived neurotrophic factor mRNA in the hippocampus. In conclusion, six repeated injections of *B. abortus* antigen induced hippocampal hypoactivity and atrophy in Balb/c mice.

Conclusion:
It is speculated that RSV is an effective agent for improving fatigue symptoms and enlarging the atrophic hippocampus, by repressing apoptosis and promoting neurogenesis, which might be one possible mechanism for recovery from fatigue.

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A Comprehensive Biochemical Model for the Pathogenesis and Pathophysiology of ME/CFS, and Effective Treatment Based on It

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Independent Researcher

Objective:
To build a comprehensive model for the pathogenesis and pathophysiology of ME/CFS that will lead to accurate diagnosis and effective treatment in clinical practice.

Methods:
This paper builds on work presented at the previous three conferences of the IACFS/ME and its predecessors. In 2004, the author emphasized the importance of glutathione depletion in the pathogenesis and pathophysiology of ME/CFS (1). In 2007, he linked this to a partial block in the methylation cycle (2). In 2009, he and a physician presented evidence from a clinical study of a treatment based on this mechanism in a private practice, which was found to produce significant benefits for most of the patients, in terms of both symptomatic improvement and normalization of lab measured parameters (3).

Results:
Since the previous conference, further progress has been made in developing a comprehensive model of the pathogenesis and pathophysiology of ME/CFS at the biochemical level, which is consistent with available research on this disorder, clinical experience, and patient health histories, symptoms, and treatment outcomes.

To the author's knowledge, this hypothesis is the only proposed model at the biochemical level that is capable of explaining the wide variety of features of this disorder in a straightforward manner. It draws together the specialized work of other researchers in epidemiology, genomics, nutrition, allopathic load, toxicology, gastroenterology, metabolism, exercise science, sleep science, gene expression, cardiology, neuroendocrinology, immunology and virology. It offers measurable biomarkers and guidance for effective clinical treatment.

This model also has the potential to mesh well with retroviral involvement in ME/CFS, owing to the known silencing of gene expression by methylation.

A significant number of patients, under the care of several clinicians, are currently receiving treatment based on this work, and most are experiencing improvement. A small number of what appear to be complete recoveries have been reported.
Conclusion: Treatment to lift the partial methylation cycle block appears to be an important component of an overall treatment protocol for ME/CFS.

1. http://www.aboutmecfs.org/Rsrch/GluAACFS04.aspx
2. http://www.aboutmecfs.org/Rsrch/GSHMethylation.aspx
3. http://www.aboutmecfs.org/Trt/TrtMethylStudy09.pdf

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Riding the CFS/ME Research Rollercoaster

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Objectives:
Research advances, such as the potential association of CFS with XMRV, bring knowledge, excitement, and scientific validation to patients, families and professionals working in this field. But these developments also have the potential to cause confusion and distress, as conflicting findings emerge and new research is published that may clarify or further muddy understanding of CFS/ME and fibromyalgia. As media attention to CFS increases as a result of this research, patients gain much-needed validation of the severity of their illness, but also find themselves having to explain to family members, friends, healthcare providers, media, and concerned members of the community how this research relates to their lives, including addressing fears associated with potential contagion.

At the same time, patients must continue to cope with the CFS rollercoaster itself, which brings relapses and remittances and demands flexibility in coping strategies, depending on their current health status. As the research rollercoaster rolls on, patients need strategies to cope effectively as they continue their daily lives, and healthcare professionals need tools to help their patients interpret the impact of research findings on their own lives.

Methods:
There are twin rollercoasters at play in CFS/ME patients' lives -- one caused by increased media and research attention and the other related to the ongoing illness and its relapsing remitting patterns. Gaining an understanding of these rollercoasters is essential in helping patients develop coping strategies for both. The Fennell Four-Phase Model of chronic illness (1. Crisis; 2. Stabilization; 3. Resolution; 4. Integration) describes a predictable passage that patients navigate on their way to defining a new self and a new life after the onset of chronic illness.

Results:
The FFPM helps patients gain new coping skills, enhances quality of life, generates meaning, and improves responses to community, medical, family, media, and other concerns.

Conclusion:
Understanding FFPM and the twin rollercoasters of CFS/ME research, as well as how they are influenced by the media, the community and health status, improves patients' ability to cope with variable patterns, and also assists clinicians in helping patients navigate complex, confusing circumstances.

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Working the Third Phase: 5 Capacities For Coping With Trauma and Loss In CFS/ME and Fibromyalgia

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Objectives:
To live a full life with CFS/ME, fibromyalgia, or other chronic illnesses, individuals and families must learn to accept their circumstances and find meaning in the experience. The arts -- music, humor, movement, writing, painting, or other methods -- helps individuals with chronic conditions develop this acceptance and meaning for enhanced coping.

Methods:
An online program was launched in mid-2010 that uses the arts to help people develop a healthy response to chronic illness. This program helps people with chronic illnesses use five capacities of improvisation that are explored through the arts and that people coping with chronic illnesses need to acquire to establish acceptance and meaning. These capacities are 1) Tolerate ambiguity, 2) Take risks, 3) Become curious, 4) Improvise, and 5) Innovate.

The program, initiated in May 2010 in collaboration with the DePaul Chronic Illness Initiative, is derivative of the evidence-based Fennell Four-Phase Model, which has established that people experience Four Phases – 1) Crisis, 2) Stabilization, 3) Resolution, and 4) Integration -- on their way to defining a new self and a new life with chronic illness. It is in the Resolution Phase where individuals begin to find meaning in their experience and develop a supportive, meaningful philosophy. Creativity and the arts are a mechanism for using improvisation to progress toward and through the Third Phase.

Results:
The tools of improvisation offer a pathway toward establishing meaning in the chronic illness experience for enhanced coping.

Conclusion:
Improvisation, the skill of top artists, can offer new ways to respond better to change. In improvisation, we use our existing knowledge and skills to create something new in an unplanned, innovative way. The web-based community offers an effective method for developing these capacities with people with disabling chronic illnesses, such as CFS/ME and fibromyalgia, who may find it difficult to travel to group meetings on a regular basis.

Relationship to Conference Theme: **A pre- and post-intervention instrument, under development, combined with the validated Fennell Four Phase Inventory, can assess how participants use the five capacities and how they influence their current Phase placement and the development of meaning.** By learning the principles of the five capacities of improvisation, patients can emerge with tools to cull prior experiences for better assessment of present circumstances and create innovative ways to respond to change.

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Supplementation of Imidazole Dipeptides Attenuates Fatigue Induced by Various Causes in Human

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Objective:
Oxidative stress is known to cause physical and mental fatigue, so antioxidants are potential candidates for anti-fatigue agents. Imidazole dipeptides (carnosine and anserine) which chicken breast is rich in, are reported to have strong antioxidative effects. This is the reason migratory birds can fly thousands of miles without rest? Here, we investigated the effect of imidazole dipeptides derived from chicken breast on fatigue induced by physical task or by daily activities in human.

Methods:
(Study I) In a double-blinded, placebo-controlled, crossover study, 17 subjects took dipeptides 400 mg/day or placebo for 29 days. As a fatigue-inducing physical task, subjects performed workload trials on a cycle ergometer at fixed workloads for 4 hours and then rested for 4 hours. We evaluated physical performance by 10-second high power test, subjective sensation of fatigue by visual analogue scale (VAS) and antioxidant and its related effects by biochemical parameters in blood and urine. (Study II) In a double-blinded, placebo-controlled, parallel study, 207 subjects who have fatigue feeling from daily activities were randomly divided into three groups; and provided with imidazole dipeptides 200 mg/day, 400 mg/day, or placebo for 8 weeks. We evaluated the subjective sensation of fatigue primarily by VAS.

Results:
(Study I) Oral imidazole dipeptides administration inhibited the impaired physical performance and the increased level of fatigue sensation, and suppressed the increased levels of the urinary oxidative stress parameters [8-isoprastane and 8-hydroxy-deoxy-guanosine (8-OHdG)] and plasma transforming growth factor (TGF)-□ by physical task. (Study II) The VAS score was significantly lower in the imidazole dipeptides 200 and 400 mg/day groups compared with that in the placebo group. The effect was remarkable especially in the 400/day group.

Conclusion:
These results suggest that the antioxidant effect of imidazole dipeptides inhibited tissue damage and attenuated fatigue by physical task, moreover the dipeptides decreased in fatigue sensation from daily activities. Imidazole dipeptides have the effects on attenuating fatigue induced by various causes, so supplementation of the dipeptides (drink, capsule, tablet etc.) is one of the promising remedies for fatigue in human.

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Whole Body Vibration Used with Positive Psychology Strategies - New and Vital Component of Multi-Modal Treatment for Decreasing the Pain of Fibromyalgia/Chronic Fatigue While Improving Happiness Levels

Dianna Campbell-Smith

From a psychological perspective, working with clients who have been diagnosed with Fibromyalgia or Chronic Fatigue can be a challenging task in that there are both difficult physiological implications as well as a tendency towards concurrent depression. Using Cognitive Behavioural Therapy (CBT) with these clients has been researched and found to be somewhat effective. There is evidence that using a CBT approach is most effective when combined with exercise therapy and at times, pharmacotherapy as well.

From an anecdotal point of view, using CBT alone does not always allow the individual with Fibromyalgia or Chronic Fatigue to move out of their pain enough to learn and integrate new ways of thinking or behaving. The pain is often described by clients as sapping all their energy such that there is little ability to undertake anything but the basics of their day to day requirements. When given homework which may well be able to help clients often say they just do not have the energy to do anything new.

The research on multimodal approaches has been encouraging. To move out of depression requires that a client focus on new techniques and strategies but in order to utilize this focus some reduction in the pain and fatigue would more easily allow integration of new materials. There are a handful of research articles looking at the value of WBV to ease pain for Fibromyalgia and Chronic Fatigue clients. One such study used exercise alone as compared to exercise supplemented with whole body vibration. The conclusion of the study showed that exercise supplemented with whole body vibration was beneficial whereas exercise alone was not. Another study concluded that WBV helped with the balance aspects often a problem with Fibromyalgia.

Further research into use of whole body vibration machines as part of a multi-modal approach is warranted. In this multi-modal approach it is suggested that clients would be taught how to use of techniques to increase their level of happiness while decreasing their experience of pain and fatigue. Given the research into pain reduction through use of wbv, as scant as it is, it suggests a number of sessions on a whole body vibration machine throughout the week. Each session would be increased from a few minutes up to ten minutes three times each week. Pain assessed on a weekly basis to ensure continued reduction would be required. Clients would learn how to integrate new ways of thinking that discover and take advantage of their own strengths such as creativity, love of learning, bravery and valour as determined from the Character Strengths (Peterson and Seligman, 2007).

The research into pain reduction through use of WBV, as scant as it is, suggests a number of sessions on a whole body vibration machine throughout the week. In addition, counseling sessions could be used to displace habitual negative thinking by helping clients to integrate positive psychology thinking and activities.

As is the case in counseling, a single style of therapy does not work for every client. Some are helped by Cognitive Behavioural Therapy, some by Narrative therapy and others may be helped by Art therapy. It is likely that in order to help a broader range of clients with Fibromyalgia or Chronic Fatigue that a number of different multi-modal strategies should be considered. Given some of the positive studies of whole body vibration, use of this equipment in conjunction with positive psychology techniques to increase happiness levels should be considered. Further research in this area is certainly warranted as anecdotal reports suggest that they may be some benefit.

Enhanced External Counterpulsation in the Treatment of Chronic Fatigue Syndrome by Improving Cardiac Output

Derek Enlander MD,
Thomas Riedman, RN,

Introduction:
The etiology of Chronic Fatigue Syndrome (CFS) is unknown and has been related to many different pathophysiological disorders including virological, immunological, neuroendocrine, genetic and psychiatric sources.[1-9] . In 2003, Peckerman and coworkers [10-12] suggested CFS may be related to impaired circulation, specially reduced stroke volume (SV) and cardiac output (CO) [10]. The more severe patients suffered from post-exertional fatigue, the more serious was their CFS, and proportionally the lower their CO. We hypothesized that a treatment that can increase CO may then improve the CFS symptoms. It has been known for many years that abnormal venous return will lead to reduced cardiac output, orthostatic tachycardia and in turn failure.[10-12]. It has been suggested that this disturbance is at a cellular or subcellular mitochondrial level. [13-21] or a carnitine metabolic problem [22-28]

Enhanced external counterpulsation (EECP) is a circulatory assist device.[15] . EECP operates by wrapping three sets of cuffs around the lower extremities, compressed during diastole to squeeze both arterial and venous blood back to the heart, increasing coronary perfusion and right ventricular filling pressure. The compression is released during systole, effectively increases peripheral arterial capacitance and lowers the impedance to cardiac ejection as well as systolic workload. The counterpulsing action to the heart by

the EECP system has been shown to increase SV, CO, systemic blood flow velocity, and shear stress acting on the endothelial cells, stimulate endothelial function, including release of angiogenesis factors that promote collateral and improve microcirculation. Currently in the United States EECP® Therapy has been FDA approved for use in unstable and stable angina pectoris, acute myocardial infarction, congestive heart failure and cardiogenic shock.

Objective:
The primary objectives of this study were to examine the changes in stroke volume, heart rate, and cardiac output measured by thoracic electrical impedance cardiography (ICG) after a course of EECP therapy in patients suffering from CFS without evidence of coronary artery disease , and to evaluate whether EECP therapy reduced the severity of CFS. EECP treatment has been shown to increase CO in patients with refractory angina, and in patients with heart failure, it has not been used in CFS patients with reasonable normal SV and CO. CFS patients with coronary artery disease were excluded from this study in order to eliminate an important variable. If there were improvements in the functional capabilities of the patients, it is due to reduction in the severity of CFS and not their cardiac functions. Another objective for this study was to identify whether there are any relationships between SV and CO and CFS severity, particularly any relations in the changes in SV and CO to changes in CSF severity after EECP treatment.

Methods Patient Selection:
This study enrolled twenty patients seeking treatment between 2009 to 2010 in a New York city clinics satisfying the Fukuda case definition of CFS by the Centers for Disease Control and Prevention National Center for Infectious Diseases and Canadian Consensus definition [16,17,18] with unexplained persistent or relapsing chronic fatigue that is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities, and concurrently suffering from four or more of the following symptoms: substantial impairment in short-term memory or concentration; sore throat; tender lymph nodes; muscle pain; multi-joint pain without swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and post-exertional malaise lasting more than 24 hours. These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue. Conditions that exclude a diagnosis of CFS include any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea and narcolepsy, and iatrogenic conditions such as side effects of medications, any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa; or bulemia nervosa, and alcohol or other substance abuse that occurred within 2 years of the onset of chronic fatigue and any time afterwards.

Study Design:
CFS severity measure: After signing an informed consent form, patients without evidence of coronary artery disease and satisfying the enrollment criteria of suffering from CFS were asked to complete a battery of questionnaires concerning their demographics, medical history, family risk factors, medications and were assigned by a physician Karnofsky Performance Status scores (KPS) to assess their CFS severity levels. KPS is a general activity and medical care requirements measure to evaluate patient's ability to carry on normal daily activity and work or require custodial care using a 0-100 point scale, ranging from 0-30 as severely disable, unable to care for self, 50-70 as unable to work but able to live at home with varying amount of assistance needed, and 80-100 as patients who were able to carry on normal activity and to work. CFS severity levels were reassessed by the physician at the end of the last EECP treatment hour.

Cardiac stroke volume and output**:** The SV and CO of each patient were measured using an impedance cardiography device (Casmed, Lifegard® ICG Non-Invasive Hemodynamic Monitor, Branford, CT, USA). The device sends out a constant electrical current via electrodes in the neck and abdominal to quantify the heart's mechanical activity by measuring the changes in impedance to the current which is proportional to the resulting change in blood volume (stroke volume) and velocity in the aorta (cardiac output) with each cardiac cycle. Patients were asked not to consume anything with caffeine for 4 hours before measurement performed in a quiet temperature controlled room in the supine position. The means of two recordings of 30 seconds data were used for analysis. Heart rates were measured using an electrocardiograph unit. The SV and CO measurements were done at baseline before the first hour of EECP and repeated post-EECP after the last hour of treatment.

Enhanced External Counterpulsation:
The treatment is administered to patients on an outpatient basis. EECP therapy systems are Food and Drug Administration (FDA) cleared for marketing in the treatment of stable and unstable angina, congestive heart failure, acute myocardial infarction, and cardiogenic shock. Patients The EECP treatment system (Vasomedical, AngioNew VI, Westbury, NY) consists of three sets of inflatable pressure cuffs wrapped around the calves, the lower and upper thighs, including the buttocks. The cuffs are rapidly and sequentially inflated, starting from the calves and proceeding upward to the buttocks at the beginning of diastole of each cardiac cycle, creating an arterial retrograde flow along the aorta towards the heart and significantly increasing blood flow to the coronary arteries at a time when resistance to coronary blood flow is at its lowest level. The inflation of the cuffs also simultaneously increases the volume of venous blood returned to the right side of the heart providing greater filling of the right and left ventricles. Just prior to the next heartbeat, when the heart begins to contract, all three cuffs simultaneously deflate, leaving an empty vascular space in the lower extremities to receive blood ejecting from the heart, thereby significantly reducing the workload of the heart. The inflation/deflation activity is monitored constantly and coordinated by a microprocessor that interprets electrocardiogram signals, monitors heart rhythm and rate information, and actuates the inflation and deflation in synchronization with the cardiac cycle. The inflation/deflation cycle is repeated for every heartbeat, increasing energy supply to the heart, improving SV and CO, while at the same time reducing the workload of the heart. Patients in this study received 35 hours of EECP treatment, one hour daily, five days per week over seven weeks for a total of 35 sessions.

Statistical Analysis:
The severity of CFS as evaluated by KPS scores as well as SV and CO measured by ICG before and after EECP treatment were compared using 2-tailed paired Student t-test. Changes in CFS severity versus changes in SV and CO were analyzed using a paired-

difference t-test. Correlation between CFS severity levels versus SV and CO were analyzed using Pearson R values as well as linear regression analysis. All data are reported as mean ± SD with p values < 0.05 being accepted as statistically significant in all analyses.

Results:
This study enrolled 20 patients, 5 males and 15 females, average age 46.4 ± 14.0 (range 29 to 75) years old. All patients had no evidence of coronary artery disease (CAD), but 35% had immediate family history of CAD. All patients reported suffering from massive fatigue during the past 9 months to 30 years, 85% with difficulty sleeping and serious depression. All patients completed the 7 weeks EECP treatment without any adverse events or complications due to the application of pressure to their lower extremities.

Effects of EECP treatment in CFS and hemodynamic functions
The severity levels of CFS as measured by KPS before and after 35 hours of EECP therapy improved significantly from 56.2 ± 8.3 to 62.1 ± 9.6 ($p<0.05$) while the SV also increased significantly from 50.2 ± 10.6 to 58.5 ± 11.9 ml ($p=0.02$), as shown in Figure 1. The heart rate did not change from 79.2 ± 10.2 before EECP to 77.7 ± 8.5 beats/min after EECP treatment. CO also increased significantly from 3.9 ± 0.7 to 4.5 ± 0.8 L/min ($p=0.017$), also shown in Figure1.

Figure 1 Changes in CFS severity andhemodynamic functions before and after EECP treatment. A. CFS severity asmeasured by Karnofsky Performance Scale; B. Cardiac Output; C. Stroke volume.

Mitochondrial Medicine for the Treatment of CFS/ME

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In 2009 we showed that 70 out of 71 patients with CFS/ME (Fukuda 1994 criteria) attending a private clinic had measureable mitochondrial dysfunction and were clearly separated from a control group of 53 normal, healthy people [1]. The dysfunction was determined by the ATP Profile, a set of 5 different biochemical measurements of white blood cells (neutrophils) and their mitochondria. The degree of dysfunction, the Mitochondrial Energy Score, correlated strongly with the functional ability of the patients as measured on the Bell CFS Ability Scale. The **Objectives** of the present audit are to see if the mitochondrial dysfunctions can be corrected by a therapeutic protocol consisting of 1) pacing, 2) changes in diet, 3) nutritional supplements known to be essential to the biochemical processes of energy transformation by mitochondria, and 4) detoxification to remove toxic heavy metals and biochemical toxins causing or associated with the dysfunctions. **Methods** After the initial ATP Profile and recording of the CFS Ability patients participated in the basic treatment protocol. Depending upon the progress of each patient and other factors, patients whose results are reported here had the ATP Profile tests carried out a second time and for 4 patients a third time. We can therefore measure changes in mitochondrial function and functional Ability during the treatment protocol. **Results** All patients improved by at least 1 unit on the Bell Ability Scale (0-10) and some by as much as 6 units. About 25% moved into the normal region in both Mitochondrial Energy Score and CFS Ability, and the strong correlation between these quantities is maintained by the treatment protocol. The results of a patient who had the ATP Profile 3 times clearly demonstrate the importance of the detoxification part of the protocol. **Conclusions** Whatever the cause of CFS/ME, mitochondrial dysfunction which can affect every cell of the body is a major factor. Improved mitochondrial function produces improved functional ability and these can be achieved by a protocol of targeting mitochondria to give them their essential nutrients and to remove toxins that attack them.

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Compassionate Use Treatment of CFS with GcMAF

Paul R. Cheney MD, PhD

Introduction:
GcMAF is a partially deglycosylated vitamin D binding protein (VDBP) also known as Gc protein. The functional change in the Gc protein caused by deglycosylation is known as GcMAF. GcMAF is extremely potent and will at very low concentrations activate, regulate and expand macrophages which are the central processing unit of the immune system and capable of modulating and controlling both the innate and cognate immune systems..

Methods:
Twenty-five CFS patients meeting the 1994 CDC criteria were selected from a national referral practice and under informed consent were self-treated with a semi-synthetic GcMAF administered by sub-lingual route. Previous reports from clinicians in The Netherlands using this commercial-grade version of human GcMAF suggested significant bioactivity and promising clinical responses in CFS cases in The Netherlands. Patients were monitored for blood chemistry, CBC, active and non-active forms of vitamin D as well as Nagalase activity. VDR polymorphisms determined from restriction enzyme products of BsmI and FokI were determined and a clinical instrument for symptom assessment of the seven key CFS symptoms was used to evaluate patient response. The protocol called for administering initially low doses of GcMAF at 20 ng SL every five days for the first 30 days followed by a q 5 day ramp to 100 ng SL using 20 ng increments. The study length was scheduled for 5 months but is being extended on a case-by-case basis.

Results:
Results are reported here for those eighteen CFS patients who have received a minimum of two months of sub-lingual GcMAF. 6/18 or 33.3% had a significant to clinically resolved response in at least two of seven critical CFS symptoms and two of those were functional cures at 80 KPS units or better. 5/18 or 27.8% failed to respond at all or even got worse over those same seven key symptoms. The remainder or 38.9% (7/18) had a mild to moderate improvement in two or more significant symptoms. A total of 72.2% (13/18) responded to GcMAF. VDR polymorphism data in 11 of 18 patients are known and the balance pending. Of these 11 with known VDR results, 3 of 4 who were non-responders were either BB or ff genotypes suggesting that if you had a BB or ff, you had a 75% chance of being a non-responder. On the other hand, there were no BB's in the best responding group of four suggesting that if you had a BB, there was no chance at all of being a significant responder or cure though there was a 33% chance of being a mild to moderate responder but only a 14% chance of being a member of the combined response group (1 chance in 7). Analysis of calcitriol levels demonstrated that there were three response patterns to GcMAF that were predictive of clinical response. All those with low to normal calcitriol to start with who then had a modest rise in calcitriol in response to GcMAF responded clinically (6/6). All those whose calcitriol was initially low to normal that did not respond at all to initial doses of GcMAF failed to respond clinically (4/4). In those with elevated initial calcitriol (>68) had a mixed response with 5 of 7 responding and 2 of 7 not responding. Initial D3 levels were variable and did not predict response nor did their response to GcMAF predict response. Nagalase activity was elevated in all study participants (average 3.4, range 1.3-6.5). 87.5% of the patients tested for XMRV were positive (14/16). In 6 of 8 with known response data, Nagalase activity declined with therapy and one patient declined to zero and is one of the recovered patients (KPS > 80).

Conclusions:
GcMAF appears to be a relatively benign and generally effective treatment for CFS. Most patients, however, had early though short bouts of what appeared to be exacerbations of CFS symptoms regardless of the eventual outcome. Two patients who were deemed responders developed clinical vitamin D toxicity later in their treatment heralded by a rapid rise in calcitriol above 90 as Nagalase dropped but responded very well to GcMAF dose reduction or elimination with no lasting effect on their previously good responses. Nagalase activity generally fell especially in the best responders and initial calcitriol response was predictive of outcome in most patients. VDR genomic data appears to also be a predictor of the relative chance of response vs. non-response to GcMAF.

FIBROMYALGIA

FIBROMYALGIA Disability: Is There Hope? Innovative Treatments From 20 Years of Experience with the Four Component Theory Approach

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Objective:
We present case studies/ case series of Fibromyalgia (FMS) patients treated with an interdisciplinary approach.

Method:
The 4 component model (Klinghardt) for treating chronic pain and disease helps to conceptualize an approach for FMS. This involves identifying and treating underlying root causes for pain and dysfunction in 4 areas: Structural – Biochemical – Psychoemotional – Neurological. This approach as a model for multi-modal/ multi-disciplinary treatment will be illustrated.

Results Structural:
A case series of 25 FMS patients treated effectively with **Botulinum Toxin-A** injections will be presented. Such injections into myofascial trigger points and tender points often do not work and may exacerbate FMS pain. Injections do work when done on a

biomechanical basis (correcting postural misalignments and upper/ lower crossed syndromes) and when combined with specialized manual therapy and exercise. (Ko G, Whitmore S et.al. J Musculoskel Pain 2007;15(4):55-66.). Preliminary results from a double-blind randomized controlled pilot study may also be presented. **Platelet-rich Plasma Prolotherapy** for sacroiliac ligament laxity were also helpful in post-traumatic (motor-vehicle accident) cases. (Ko G. Pract Pain Manage 2010;10(7):55-68)

Biochemical:
Case studies of FMS-CFS patients improved with **Functional Medicine and Bioidentical Hormone replacement therapy** will be presented. This includes the use of omega 3 fatty acids (at a high dose) to improve pain and mood. (Ko G, Arseneau L et.al. Clin J Pain 2010; 26(2):168-72.

Psychoemotional:
A FMS case study using **EEG biofeedback / neurotherapy** will be presented. This patient was followed over 5 years and had significant amelioration of pain, improvement in "fibrofog" and in sleep. (Ko G, Gottfried B et.al Crit Rev Phys Rehabil Med 2005;17:1-30)

Neurological:
Case series of recalcitrant FMS patients with allodynia who responded to unique multimodal combinations of neuropathic pain medications will be presented. This included combinations of Pregabalin, SNRIs, tramadol and **cannabinoids.** (Hum A et.al. Pain Res Manage 2008;13:137). Topical medication use from essential oils (J Musculoskel Pain 2007;15(1):11-20) to compounded pain gels will be described as well.

Conclusion:
These cases demonstrate the diversity in assessment for underlying causes and the need for individualized treatment in FMS. Randomized clinical trials may need to focus on specific subgroups of FMS patients to demonstrate clinical effectiveness.

You're Too Sick to Work: Messages about Fibromyalgia and Paid Work in Information Materials on the Web

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Messages about fibromyalgia (FM) infuse clinician-patient relationships. Both parties bring these messages into their understandings of FM: its diagnosis, symptoms, treatments, and prognosis. This poster will describe a study that examined messages about FM in information targeted to people with fibromyalgia on the Web. It is important to understand how these messages shape the clinical relationship: First, if clinicians and their patients develop an awareness of these messages, they can examine their usefulness for each individual patient care plan. Second, understanding these messages can help foster trust in the clinical relationship, thereby promoting clinician-patient collaboration to improve treatment efficacy. This trust and collaboration can reduce the likelihood of conflicts between clinical and lay understandings of FM.

Objectives:
This study examined messages about doing paid work with fibromyalgia (FM) in information materials targeted to people with FM.

Methods:
This qualitative study used Critical Discourse Analysis to examine text in self-help, rehabilitation, and medical websites that women with FM in the Canadian province of Ontario might access in seeking information.

Results:
Many of the messages about FM in information materials offer little hope for feeling better and returning to work. Indeed, few information materials mention work. Materials that do mention work focus on individuals' responsibility for managing their FM in the workplace, rather than accommodation of FM-related disability by employers.

Conclusion:
Staying in the workforce offers women with FM many benefits, among them decent income, sense of self-worth, social relationships, daily routine, and distraction from pain. Encouragement to remain in the workplace, or to return after short-term disability leave, is needed. Workplace accommodations of FM-related disability may be required.
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CLINICAL

Working Successfully With Patients Who Have Contested Conditions: The Case of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Objectives:
1. To provide an understanding of the impact on the therapeutic relationship of ME/CFS being a contested condition - one in which there is no proven etiology, diagnostic test or treatment.
2. To recommend solutions to the challenges and misunderstanding that arise in the relationships between patients with ME/CFS and their health care practitioners as a result of the contested status.

Methods:
Non-systematic literature review and clinical experience.

Results:
Therapeutic relationships between patients with ME/CFS and their medical practitioners are impacted by contextual issues including: debate about causality, lack of recognition, and lack of objective diagnostic markers. These issues lead to common therapeutic challenges including: debate over validity of the condition, the need to differentiate ME/CFS from primary psychiatric disorders, frustration due to lack of symptom improvement, altered power balance between the patient and practitioner, interaction with patients who feel unheard, and the need to close the gap between needed and available services. Strategies which deserve further research include: keeping an open mind, clarifying symptom profiles, collaboratively searching for hope, clarifying expertise of patient and practitioner, listening to the whole story and building a coalition to advocate for needed services.

Conclusions:
Identifying and openly discussing contextual issues which impact the therapeutic relationship allows patient and practitioner to form a working relationship against the illness and societal stigma rather than fighting each other. This collaboration may improve the quality of therapeutic relationships thereby improving patient care and outcomes.

Key words: Myalgic Encephalomyelitis, Chronic Fatigue Syndrome, therapeutic relationship, counseling, contested conditions
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Chronic Fatigue Syndrome – Three Case Studies Concerning the Very Severely ILL

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Objectives:
Chronic fatigue syndrome (CFS) often leads to extensive problems with occupational performance, and some get bedridden for a period of time. No studies so far have focused on the very severely ill. This study focuses therefore on CFS patients', as well as their relatives' and health care workers' understanding of how CFS patient' can be helped to prevent them from becoming bedridden and to promote improvement over time.

Methods:
Semi-structured interviews were used for data collection. The sample consists of three women, and from each of these women: One close relative or friend, and one health care worker, a total of 9 participants. All three patients met the CDC criteria for CFS. Anita (age 35), Sarah (age 44) and Helen (age 48) were totally bedridden from 15 months to 2,5 years. Sarah and Helen had a mild degree of CFS at the time they were interviewed, while Anita still had a severe degree of CFS.

Results:
Anita, Sarah and Helen had vague, fluctuating symptoms, and experienced an increasing intolerance for physical and mental activity. Over-exertion caused deterioration over time. When they got diagnosed with CFS, Helen was already bedridden. Sarah and Anita continued with over-exertion and got bedridden after some time. While bedridden they learned that it was important to be nursed by a few persons, according to routines they had agreed upon, and with respect for their symptoms and needs. They needed above all peace of mind and a feeling that they and their family were taken care of, so that they could use all their energy on getting better. When they started to feel better, they mobilised themselves with the support of health care workers and others, but in their own pace. They started at a very low activity level, but their intolerance for physical and mental activity improved over time. Pacing activities, energy conservation, rest/relaxation, lower expectations to themselves, stress management, social support, changes in nutrition, as well as acceptance improved their occupational performance over time. Sarah got much better after Lightning Process, while Anita just had a temporary effect. They all needed psychological help to cope with their illness-experiences. The patients' husbands, children, and close friends were affected by the illness too. Husbands and close friends got an

overload of tasks, obligations and concerns, while the children were concerned about their mothers' condition and experienced that both their parents became less available. The situation deteriorated for Anita and Helen, and their families, while waiting for adequate help. Some of their children needed professional help to cope with psychological reactions. Sarah and her family got adequate help as soon as Sarah got bedridden. She stabilised and improved much quicker, and her family members did cope much better.

Conclusion:
Diagnosing CFS at an early stage may prevent deterioration over time. In addition, patients and their families need information and help to cope with CFS in an adequate way. Those who are able to avoid over-exertion stabilise and improve over time. At the ME/CFS-centre, a multidisciplinary team applies the results of this study to give advice to patients, their families and health care workers about how to deal with CFS at all stages of the illness course.

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Healing On The Spiritual Path Through The Teachings of Bruno Groening - Medically Verifiable: Three Documented Healings of ME and Two Documented Healings of Fybromyalgie

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In a time of world-wide health crisis with steadily growing numbers of chronically sick people, an interest in handed down traditional healing is growing. Natural healing, Homeopathy, Acupuncture, Phytotherapy and others have achieved ever growing significance in the last decade in medical practice. But also the oldest form of healing, the picking up and passing on of life energy or bio-energy, very often referred to as spiritual healing, finds more and more attention among medical specialists. Already in the 50's The British Council of Medical Doctors stated the fact that, "through spiritual healing the regaining of health is possible, which by today´s perception must be looked at as inexplicable."[1] Since that time more and more hospitals of the Public Health Service have opened their doors to spiritual healing. The happenings around Bruno Gröning (1906-1959) in Germany, who is regarded as one of the most significant healers, has become the foundation-stone for a unique work of enlightenment by doctors of many countries in our time.[1,2] Thanks to the systematic work of our working group a great number of medically inexplicable progressions of healing from the most varied diseases could be recorded.[3,4,5] Documentation is taking place world-wide by means of detailed recordings and analyses of the existing diseases and of the changes that have led to the healing. By means of a certain physical and mental attitude it was possible for the observed persons, mostly after a few minutes to sense a light feeling of energizing in their bodies. Often there occurred characteristic reactions in the body as a forerunner to the healing. It was interesting to observe in many cases an increase in the existing symptoms or pain appeared mostly in the exact topographic region of the affected organ in the body. Frequently it happened that in clear timely connection with these reactions chronic disorders ceased to exist. It is interesting that these phenomena have been described by such important representatives of medical science of the last centuries, such as Paracelsus (Switzerland), and by the well known European doctor of the beginning of modern times, Hahnemann of Germany, the founder of Homeopathy. Similar knowledge exists in the Asian culture. The perceptions of our working group are presented in publications, in congresses, in different universities with medical students, and passed on in public lectures world-wide. In the last decade over 100.000 people in more than seventy countries have attended these lectures.The Focal point of the lecture will be the personal healing report of Mrs Anneke Hagen-de Waal from Germany. Mrs Hagen-de Waal recieved the healing after seven and a half years of suffering by putting into practical terms the teachings of Bruno Groening. This particular healing and two additional healings of ME and two healings of Fybromylagie will be presented and commented on by a medical doctor.

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Development of Standardized Patient Scenarios as a Teaching Tool for ME/CFS

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Objectives:
1. To describe the process of developing two "standardized patient" clinical teaching tools for ME/CFS 2. To evaluate the effectiveness of these tools in a mixed health care professional audience attending a educational workshop on ME/CFS.

Methods:
The process started with two focus groups of physicians who were unfamiliar with ME/CFS. The groups identified their top learning priorities with regards to ME/CFS. Clinical cases were developed to address these identified needs based on the Canadian Consensus Guidelines. The cases were then "workshopped" extensively by expert clinicians and patient focus groups and standardized patient trainers. The final standardized scenarios will be presented in vivo at an accredited CME medical education workshop April 30, 2011. Evaluations of the April 30th, 2011 workshop will provide data on the acceptability of these tools to health care professionals.

Results:
Patient feedback to the two scenarios: 1. diagnosis and 2. symptom management was extremely positive. Patient input ensured that the scenarios reflect that ME/CFS is a biomedical condition which due to it's severity, variability and uncertain prognosis can cause depression, anxiety and stress. They also stressed the importance of clinicians asking about the lived experience of patients with ME/CFS. This is a qualitative evaluation of new teaching tools. The presentation will include verbatim comments from participants, evaluation data and may include video clips.

Conclusions:
These standardized clinical scenarios are well received by patients with ME/CFS and have promise as teaching tools for health care professionals

Key words: Myalgic Encephalomyelitis, Chronic Fatigue Syndrome, medical education, standardized patients

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Thyroid Malignancy Associated with Severe Cognitive Dysfunction, Cortical & Subcortical NeuroSPECT changes in Patients Presenting with a Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)

Byron M. Hyde, M.D.
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In our investigations, thyroid malignancy in ME/CFS patients greatly exceeds the normal incidence in any known subgroup. Various published studies over recent years have suggested an increasing incidence in the general public from 15 up to 30 per 100,000. However in 100 consecutive patients with M.E./CFS evaluated in our clinic by total body investigation, the malignancy incidence excedes 6,000 per 100,000. Each patient's evaluation includes ultrasound and needle biopsy of suspicious nodules. Malignant nodules are usually noted as solitary, hypervascular nodules 1 cc in diameter or larger, although all hypervascular nodules have been biopsied. We suggest that as part of their investigation, all ME/CFS patients should be examined by thyroid ultrasound for evidence of thyroid pathology and malignancy. Thyroid pathology may be missed in this group of patients if investigation relies only upon serum testing for TSH, FT3, FT4, microsomal and thyroglobulin antibodies, which are usually normal in the case of malignancy. Unfortunately, corrective treatment by surgical and / or nuclear techniques plus appropriate hormonal replacement medication has not improved the symptoms of fatigue, cognitive and pain syndromes nor the SPECT brain changes. A newly recognized syndrome may exist in ME/CFS patients characterized by: (a) thyroid malignancy, (b) persistent pathological cortical and subcortical SPECT brain scans (NeuroSPECT), (c) failure of thyroidectomy surgery and hormone replacement to correct the fatigue syndrome, (d) an unusual high incidence of cervical v ertebrae pathophysiology. The question remains unresolved as to whether the NeuroSPECT changes consistent with a chronic low grade encephalopathy that we associate with cognitive dysfunction, precedes the thyroid malignancy and may provoke increased malignancy. A long term follow up of these M.E./CFS patients with NeuroSPECT evidence of encephalopathy but without thyroid malignancy is in progress to evaluate whether this group of patients is more prone to developing thyroid and other malignancies.

We have also found a significant higher rate of development of all thyroid disease in this same group of M.E./CFS patients. This and other anomalies will be discussed with SPECT brain images of these patients.

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Canadian Techniques of Investigation of M.E. / CFS & FS Patients and Resulting Anatomical, Patho-Physiological and Genetic Findings

Byron M. Hyde, M.D.
Allie Chor: Research Assistant

The Canadian health care system, provides free physicians, investigation and non-pharmaceutical treatment to all patients. Tests include all blood, urine, tissue and technological testing such as cardiovascular, ultrasound, MRI, PET, SPECT, Nerve Conduction, Radiological or Nuclear Medicine examinations. Any corrective surgery, procedural care or hospitalization are also provided free of charge. Unlike in the UK, Australia and many other European countries any physician in Canada can order any test available in Canada. Unlike US physicians, we do not have to ask whether the patient has insurance coverage since all are covered.

M.E. and CFS Patients: This system allows an understanding of the patho-physiological basis of why a patient is chronically ill with either a fatigue, cognitive or pain syndrome or a combination of these symptoms. This free assessment has resulted in a significant difference in the understanding of the cause of M.E. and CFS illness.

Chronic Fibromyalgia & Fibromyalgia Syndromes (FS): Due to long term follow up and the ability to do significant testing over years at no cost to the patient, we have shown that a majority of chronically ill fibromyalgia patients actually suffer from developing rheumatoid, arthritic, structural, medication induced or genetic illnesses.

How to examine & test M.E. and CFS patients: This paper will demonstrate the techniques and difficulties of total body (system and organ) assessment over the past 26 years. The paper will demonstrate the reasons why patients with M.E. and CFS, irrespective of the initiating cause(s), remain chronically ill with brain and fatigue dysfunctions.

The Multiple Pathologies of M.E., CFS and FS Patients**:** This paper will also demonstrate the findings which suggest many patients diagnosed with M.E. or CFS are treatable and many require more specific treatment research.

Access to a free investigational template will be provided to all symposium members

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Ten Important Facts Derived from M.E./CFS History That Can Improve M.E./CFS Research

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An increasing number of world experts are contributing to M.E./CFS research, but many do not have a good understanding of the historical lessons already learned in these epidemic illnesses. A better understanding of M.E./CFS history will contribute to more efficient research in understanding, virology, cognitive and brain dysfunction. For instance, a recent published discovery of an abnormal protein in spinal fluid of CFS patients was already demonstrated by Harvard's Dr Charles Poser in 1990.

For 26 years, since 1984 to 2011 my medical practice has been limited to the full time investigation of M.E., CFS & FS patients. During the earlier period I visited multiple epidemic sites, interviewed & examined patients & discussed & at times resided with many of the chief investigators of these epidemics. The patients & epidemic sites personally investigated include: (a) Los Angeles County General Hospital epidemic 1934, (b) Akureyri Epidemic Iceland 1947-48, (c) Royal Free Hospital Epidemics 1955-1956, (d) Cumberland Epidemic 1955, (e) Newton-le-Willow Epidemic 1956. The earlier researchers include Drs. Melvin Ramsay, Betty Dowsett, John Richardson, Eleanor Bell, James Mowbray, Andrew Wallis family, J. Gordon Parish. W.H. Lyle, Charles Poser, Alberto Marinacci, Ismael Mena, Sheila Bastien, Alexis Shelokov, Peter Snow & Clem Boughton to name a few.

Dr Byron Hyde will review ten important largely forgotten facts learned from 26 years of investigating various world epidemics and questioning the experts who investigated these epidemics that will assist M.E., CFS & Fibromyalgia researchers..

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Are Walls Better Than ill-Defined Bridges? Revisiting Descartes' Biomedical Model From a Biopsychosocial Perspective in Chronic Pain Due to Osteoarthritis

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Introduction:
Biopsychosocial and biomedical model are two remarkably different and most argued perspectives on chronic pain. In contrast to biomedical model, biopsychosocial model facilitated greater understanding of the contribution of mental and social health to chronic pain experience. This led to a theoretical and practical shift from traditional unidimensional towards integrated models of chronic pain. However, these multidimensional models have failed to offer a uniform definition, classification system, diagnostic criteria or treatment strategies to manage chronic pain especially in that observed in osteoarthritis (OA) population. Instead, it has

faced criticism for ill-defined integrating links which foster no standardization of research or clinical practice and therefore no future directions.

Objectives:
The purposes of the paper were i) to re-visit the philosophical underpinnings of the Descartes' biomedical model, ii) to discuss and critique the contributions of the biopsychosocial model over the biomedical model in chronic pain related to OA.

Methods:
A topical review of the studies concerning biopsychosocial and/or biomedical model and chronic musculoskeletal pain published in peer reviewed journals since 1960 was conducted. Patient population was restricted to osteoarthritis in the elderly age group.

Results:
Re-examining Descartes' philosophy reveals that much of the interpretation of his work does not reflect or elucidate the aspects of chronic pain as experienced by those with OA. Using the example of chronic pain in OA, this paper proposes that biopsychosocial model is essentially biomedical model with some additions and does not offer any significant advancement over the biomedical model.

Conclusion:
Efforts are to be directed towards a more absolute conceptualisation of chronic pain with collaboration of researchers and trans-disciplinary healthcare teams leading to explicit models that could possibly unravel the mind body dilemma in healthcare field.

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INFECTIOUS DISEASE RESEARCH

High-Throughput 16s rDNA Sequencing Reveals Alterations of Intestinal Microflora in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients

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Objectives:
Human intestinal microflora plays an important role in the maintenance of host health by providing energy, nutrients, and immunological protection. Intestinal dysfunction is a frequent complain in ME-CFS patients, and previous reports suggest that dysbiosis, i.e. the overgrowth of abnormal populations of bacteria in the gut, is linked to the pathogenesis of the disease. Recently developed technologies are able to provide a comprehensive overview of the gut bacterial populations (metagenomics approach). We used high-throughput 16s rDNA sequencing to investigate the presence of specific alterations in the gut flora of ME-CFS patients from Belgium and Norway.

Methods:
39 ME-CFS patients and 35 healthy controls were included in the study. Bacterial DNA was extracted from stabilized stool samples and PCR amplification was performed on conserved 16S rDNA regions. PCR amplicons were then sequenced using Roche FLX 454 genome sequencer (6000-10000 sequences per sample). Bacteria were classified by phylum, family and genus; diversity indexes (Chao and Shannon) were also calculated. Data were analyzed using Mann-Whitney test and step-wise linear discriminant analysis.

Results:
ME-CFS patients presented altered levels of specific bacterial populations: Prevotella, Asaccharobacter, Lactonifactor, Eubacterium. Linear discriminant analysis showed that a significant ($p<0,001$) discrimination between control and patient populations could be achieved by using a combination of Asaccharobacter, Turicibacter, Ruminococcus and Enterococcus as variables. Differences could be seen between males and females, as well as between people from different geographical origins (Belgium vs. Norway).

Conclusions:
ME-CFS patients present significant alterations of their gut flora composition. More research has to be done to fully understand how intestinal bacteria can contribute to the pathogenesis of the disease (production of toxic metabolites, interaction with host immune cells…), but also how host factors (especially genetic factors) and external factors like diet or viral infections can influence the response of the body to gut bacteria. Metagenomics is a useful tool to diagnose dysbiosis in ME-CFS patients and to help designing treatments based on gut flora modulation (antibiotics, pre- and probiotics supplementation).

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Retrospective Analysis of a Cohort of Internationally Case Defined Chronic Fatigue Syndrome Patients in a Lyme Endemic Erea

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Introduction:
Goals:

a. To determine the prevalence of seronegative Lyme in a CFS clinic in a Lyme endemic region, that actually represented persistent borrelial infection.
b. To determine if antimicrobial intervention as an integral part of treatment was able to assist in the delineation of this potential cohort.

Chronic Fatigue Syndrome represents a symptom complex often including in addition to clinically significant fatigue, the co-morbidities of fractured nonrestorative sleep, endocrinopathies [such as decreased cortisol production], autonomic dysfunction [such as neurally mediated hypotension and postural orthostatic tachycardia] [8]. It is the interpretation of the author that this "CFS like complex" represents a valid model for the management of many patients with chronic persistent Lyme infection [9].
The adverse societal impact of CFS was reported by Reynolds et al in 2004. Estimates were of a 37% decline in household productivity and a 54% reduction in labor force productivity among people with CFS. The annual total value of lost productivity in the United States was $9.1 billion which represents about $20,000 per person with CFS or approximately one-half of the household and labor force productivity of the average person with this syndrome [2]. The following data would suggest that we have the capacity to better characterize a substantial number of "CFS" patients as having "seronegative" persistent Lyme infection for which adjustments in intervention are shown to improve outcomes. Thus, we are attempting to provide evidence to the etiology of Chronic Fatigue Syndrome, while also providing input as to the clinical manifestation of persistent Lyme infection.

The management of Lyme disease regarding diagnosis and treatment unfortunately is wrought with controversy. There is one evidence based school of thought that Lyme disease is easily diagnosed and easily treated [10-11]. This set of guidelines has had questions raised as to the quality of the evidence with which the recommendations have been generated: "…The IDSA guideline recommendations are primarily based on low-quality evidence derived from nonrandomized studies or expert opinion. These findings highlight the limitations of current clinical infectious diseases research that can provide high-quality evidence…"[12-14]. There is an alternative, evidence based position that suggests that the diagnosis of Lyme disease is associated with insensitivities and that the management of those identified with this condition regularly have protracted, and relapsing courses often requiring prolonged antimicrobial therapy [15].

Methods:
An arbitrary date was chosen such that all patients registered in the database of the practice of the PI, which is located in the Lyme endemic area of Northern Virginia area were reviewed. The diagnosis of clinically significant fatigue > 6 months was chosen to filter the patients subsequently chosen. The charts of these individuals were reviewed to determine:

A. Qualification for fulfilling the International Case Definition for CFS including [1,8]:
    1. Appropriately guided causes of chronic fatigue have been ruled out [1] [including screening serologies for Bburgdorferi, vis a vis the recommended "two tiered" system. [10]
    2. Secondary criteria: CFS symptom criteria (0-absent/10-profound) achieving at least
        - ⇨ 4 of the following 8 secondary criteria
        - ⇨ 5 of 10 in a severity scale [0 being absent, 10 being most severe]
        a) impaired memory or concentration
        b) sore throat
        c) tender neck or axillary lymph nodes
        d) myalgia
        e) arthralgias
        f) new headaches
        g) unrefreshing sleep
        h) post exertional malaise
B. Possibility of "seronegative" Lyme disease as determined by one or more of the following criteria:
    a. Seropositivity to ANY highly specific band to Bb IgM or IgG (23-25, 31, 34, 39, 83-93) [16-20]
    b. And/or presence of any tick borne "co-infection" such as Babesia, Bartonella, or Ehrlichiosis species[21-32]
    c. And/or a low CD57 [33]
    d. And/or an elevated C4a [34]
    e. And/or an elevated C6 peptide [35-37]
C. Initiation of antimicrobial intervention for those suspected of having seronegative Lyme disease.
D. Assessment of clinical course was determined by way of a symptom questionnaire attached. To assess construct validity, this metric was given to two independent clinical researchers with instructions to assign each item on the value of the question asked, for which there was agreement and thus felt to be validated.

    Completed contemporaneously at each office visit by the study patient, this questionnaire provided a numeric value of the patient's complaints that could then be tracked serially with a high score representing a more symptomatic individual. Taking the highest score and comparing to the lowest score, we were able to determine the relative therapeutic impact of intervention employed. Antimicrobial intervention was varied but included such protocols as biaxin/omnicef and

doxycycline/zithromax. Given that this was a retrospective analysis, antimicrobial management was not controlled, but chosen at the point of care.

E. At least one visit after initiation of antimicrobials to allow for a relative assessment of therapeutic intervention.
F. IRB approval: WIRB Study #1121119

RESULTS:
All patients fulfilled the international case definition of CFS [1], including a negative Lyme disease serology. Of the total 210 included in the analysis, 209 or 99% were felt to represent a high likelihood of "seronegative Lyme disease." Initiating various antimicrobial regimen [in conjunction with managing co-morbidities in this uncontrolled study], involved at least a 50% improvement in clinical status in 130 or 62%. Although not achieving the 50% threshold according to the criteria discussed, another 55 patients subjectively identified a beneficial clinical response to antimicrobials, representing a total of 188 or 88% of the total identified as having a high potential for seronegative Lyme disease.

Analysis of PI patients	N	% total	% seroneg Lyme patients
International Case Defined CFS [8]	210	100%	
"seronegative" Bb screen, POSITIVE alternative criteria [see B above]	209	99%	100%
equal to or > 50% clinical improvement	130		62%
<50% improvement but still clinically significant	55		26%
total clinically significant improvement	188		88%

Demographics:
Seronegative Lyme patients:

	women	men
Ethnic background		
Caucasian	158	44
African American	2	1
Hispanic or Latino	0	1
American Indian/Alaskan	0	0
Asian	0	0
other	1	0
unknown	3	0
average age:	42	38

The one patient who did not fit the seronegative Lyme criteria was a 46 year old Caucasian woman.

Antimicrobials employed:
Recognizing that the infectious process to which we are alluding is often polymicrobial [including Borrelia, Babesia, Bartonella species and others], several antimicrobials were often employed. In addition, there were frequently relapses in many cases when antimicrobials were entirely withdrawn. The duration of treatment was generally adjusted by the patient's clinical response and was quite variable. Examples of regimen associated with at least a 50% clinical improvement include:

Agent	Dose	Duration [months]
doxycycline	200mg bid	5
with zithromax	500mg/d	9
Ceftin	1.0gm bid	8
with Ketek	400mg bid	7
Zithromax	250mg to 500mg/d	4
Mepron	750mg bid	2

Biaxin	500mg bid	12
Mepron	750mg bid	6.5
Amoxicillin	875mg bid	5.5

Comments:
Precedence exists in the literature regarding the need for prolonged antimicrobial management in certain infections:

a) Mycobacterium tuberculosis treated for 6-18 months with multiple agents [38]
b) Nontuberculous mycobacteria
    a. such as *Mycobacterium marinum* are likely to require at least 6months of treatment [39]
    b. And disseminated *Mycobacterium chelona* treatment may involve a combination of oral and intravenous antibiotics administered for 6 to 12 months.[40]
c) Hansen's Disease [Leprosy] protocols up to 2 years [41-43]

Discussion:
It is our overarching hypothesis that a potentially substantial proportion of patients with what would otherwise be consistent with internationally case defined CFS in a Lyme endemic environment actually have a perpetuation of their symptoms driven by a persistent infection by Borrelia burgdorferi. By treating this cohort with appropriately directed antimicrobials, we have the ability to provide improved intervention. In essence, by improving our ability to characterize this cohort of individuals as having active Lyme disease and treating them accordingly, we are more likely to improve outcomes.

Questions have been raised that the therapeutic gain seen by use of antimicrobials in the aforementioned setting is DUE to their anti-inflammatory affects. In addition to their antibacterial properties, it is clear that many antimicrobials also have anti-inflammatory properties. Examples would include tetracyclines [44,45], macrolides [46,47] and quinolones [48,49]. With respect to the above clinical assessment, there may very well be a component of therapeutic gain, as likely seen in ANY OTHER infectious process by way of the anti-inflammatory effects of some of the agents. However, to suggest that this is the ONLY mechanism of action, we believe is a mischaracterization:

1. Virtually all patients with pain syndromes [including arthralgias/arthritis, headache, myalgias, etc] had already taken over the counter NSAIDS without adequate therapeutic gain.
2. It is the contention of the authors that there must be an anti-infective component of these agents because of the frequently associated "Jarisch-Herxheimer" reactions [50,51]. In essence initiation or increase in antimicrobials being associated with what is usually a self limited increase in symptoms [such as headache, arthralgias, etc]. This phenomenon is felt to "caused by release of endotoxin-like material from the spirochete as well as cytokine elevation." Unless there is a cidal effect an anti-inflammatory theoretically should not generate this response.

Potential limitations:

1. This is a retrospective study which does not allow for control of confounding variables, such as treatment choice or management of co-morbid conditions such as fibromyalgia or fractured nonrestorative sleep. On the other hand, this sample may be more generalized to patients seen in actual practice as such patients were not excluded. Future research should assess for such variables so that they can be statistically controlled.
2. The study sample represents those living in an endemic environment for Lyme disease and thus cannot be directly extrapolated to non-endemic regions. However, this must be qualified by recognizing that with our mobile society, it is quite conceivable that individuals not "living" in a Lyme endemic region that by vacationing, or other reasons, may very well have intermittent exposure to Lyme endemic regions.
3. There may be a selection bias in seeking a clinician known to have expertise in chronic fatigue and Lyme disease management.
4. In addition, although likely a lower relative risk regions that are not considered "endemic," there is still likely some level of exposure risk. As such consideration for this paradigm would still be appropriate.

Additional suggestions for future research:

1. Obtain microarray analysis for Borrelia burgdorferi on the "seronegative" Lyme patients for which collaboration is being pursued.
2. Perform a prospective randomized placebo controlled, trial for which a protocol and IRB are already in place, for which funding is being pursued.

Disclosures: The author has been a member of the International Association of Chronic Fatigue Syndrome since the early 90s and of the International Lyme and Associated Diseases Society since 2005.

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IMMUNOLOGY

Exercise Effects on Biomarkers in GWI, CFS and Healthy Controls

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Objective:
To determine the effects of an aerobic exercise challenge on potential biomarkers in Gulf War Illness (GWI), Chronic Fatigue Syndrome (CFS0 and healthy controls (HC).

Methods:
37 GWI [73% male], 23 CFS [52% male] and 36 HC [75% male], age between 28 and 57 were recruited from the Miami VA Medical Center. Inclusion criteria for GWI included deployment to Operation Desert Storm between 8/8/1990 and 7/31/1991, with one or more symptoms present after 6 months from at least 2 of the following: fatigue, mood and cognitive complaints and musculoskeletal complaints. Subjects were in good health prior to 1990, and had no current exclusionary diagnoses that could reasonably explain the symptoms. Subjects taking medications with potential impact on immune function were excluded. CFS subjects met the Canadian case definition. Control subjects were Gulf War era sedentary veterans and were matched to GWI subjects by age, BMI and ethnicity.The exercise test was administered using a Vmax Cardiopulmonary Exercise Instrument, Sensor-Medics fully automated cycle ergometer, and SensorMedics Stress ECG. Subjects pedaled at an initial output of 60 watts for 2 minutes, followed by an increase of 30 watts every 2 minutes until the subject reached: 1) a plateau in maximal oxygen consumption (VO2); 2) a respiratory exchange ratio above 1.15; or 3) the subject stopped the test. Prior to the exercise challenge subjects sat quietly for 30 minutes before 1st blood draw. Second and 3rd blood draws at VO2 max and at 4 hrs post exercise. Biomarkers included plasma cytokines, measured using a multiplex assay; plasma soluble CD2 (sCD2) by ELISA; CD26 expression on CD2+ lymphocytes (%CD26+CD2+) by flow cytometry; surface molecules of CD26 per CD2+ lymphocyte (rMolCD26/CD2+) by quantitative flow cytometry; plasma neuropeptide Y (NPY) by RIA; natural killer cell cytotoxicity (NKCC) by bioassay and molecules of intracellular perforin per NK cell by quantitative flow cytometry. The non-parametric Friedman test for repeated measures assessed the significance of changes in the expression of biomarkers for each group at each time point.

Results:

Biomarker	Friedman Test Result: (significant values of *p* in bold)		
	GWI	CFS	HC
sCD26 (ng/mL plasma)	**0.057 (↑)**[a]	0.530	0.338
%CD26+CD2+ T &NK cells	**<.000 (↓)**	**<.000 (↓)**	**<.000 (↓)**
rMolCD26/CD2+/ T & NK cell	**0.015 (↑)**	**0.004 (↓)**	**<.000 (↑)**
NPY (pMol/L plasma)	**0.049 (↑)**	0.436	**<.000 (↑)**
IL-1α (pg/ml plasma)	**0.063 (↑)**	0.590	0.600
IL-5 (pg/ml plasma)	**0.038 (↑)**	0.496	0.218
IL-6 (pg/ml plasma)	0.675	0.607	**0.008 (↑)**
IL-10 (pg/ml plasma)	**0.033 (↑)**	0.857	**0.001 (↑)**
IL-12p70 (pg/ml plasma)	0.219	0.354	**0.002 (↑)**
TNFα (pg/ml plasma)	0.150	0.624	**0.007 (↑)**
rMolPerforin/NK cell	**<.000 (↑)**	**0.012 (↑)**	**<.000 (↑)**
NKCC (%)	**0.040 (↑)**	**0.023 (↑)**	**0.001 (↑)**

[a]direction of change

Twelve biomarkers were identified as having significant changes in one or more of the groups examined as a result of aerobic exercise. Soluble CD26 levels in plasma were elevated in GWI at peak exercise. % of CD26 on lymphocytes in GWI and control subjects decreased in all groups. # of CD26 molecules on each CD2+ lymphocyte was higher for GWI and HC, but lower upon exercise in CFS. NPY rose in both controls and GWI; there was no exercise response in CFS. While a strong response occurred in 4 of 6 cytokines in controls, only 3 of 6 cytokines were elevated in GWI. CFS patients had no significant response to exercise. Both measures of NK cell function, perforin and cytotoxicity, were elevated in the 3 groups.

Conclusions: Biomarker measurement during the course of an aerobic exercise challenge indicates major differences among GWI, CFS and HC likely to enhance our understanding of these complex disorders.

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Vitamin D and IL 10 in Chronic Fatigue Syndrome

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Background:
Chronic Fatigue Syndrome (CFS) is considered a state of chronic inflammation.
Vitamin D inhibition of pro-inflammatory processes has been observed and one of the proposed mechanisms is the ability to modulate T regulatory cell (Treg) function. Also a possible effect of vitamin D in IL-10 pathway (which is an anti-inflammatory cytokine) has been shown as IL-10-secreting T regs can be induced following activation in the presence of vitamin D.

Objective:
To determine vitamin D levels in a group of CFS patients and also evaluate if this level correlates with IL-10 levels.

Methods:
Data of subjects evaluated at the Center for Multidisciplinary Research on CFS, was obtained in a cross-sectional manner, from January to June 2010, in which vitamin D and IL-10 were measured in their first visit before therapeutic intervention.
Collected data include demographics (age, gender), vitamin D and IL-10 levels and natural killer cytotoxic activity.
Vitamin D deficiency was considered if its level was less or equal to 30ng/mL (75nmol/L), based on the recommendation of the International Osteoporosis Foundation
Statistic analysis included descriptive statistics and correlation calculated with Pearson's r.

Results:
There were 54 people (13 men and 41 women) with pertinent available information, age 47.78±14.9, vit D 33.68 ±16.6, IL-10 15.7±16.1, nk activity 9%±5.6. The prevalence of vitamin D deficiency in this group was 57.4% (46.2% in men and 58.5% in women). Correlation between vitamin D and IL-10 levels was 0.228 (p=0.048). There was no correlation between vitamin D and NK activity or age in the studied group.

Conclusion:
The prevalence of Vitamin D deficiency was 57.4% and there was a significant correlation between VitD and IL-10 levels in this group of CFS patients.
Clinical randomized-controlled studies that evaluate the immunomodulatory effect of vitamin D in patients with CFS are necessary.

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Abnormal Cytokine Levels in Patients with CFS Regardless of Metabolic Syndrome

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Background:
Metabolic Syndrome (MetSd) is a known risk factor for significant morbidity and mortality, including cardiovascular and cerebrovascular disease. It has been described that inflammation plays an important role in the pathogenesis of MetSd, with upregulation of both TH1 and TH2 cytokines. Previous studies have shown that patients with CFS were 2-fold as likely to have metabolic syndrome compared with healthy controls.

Objective:
To compare cytokine levels in patients with Chronic Fatigue Syndrome (CFS) with and without metabolic syndrome.
Methods: With a cross-sectional study design, we evaluated the data from participants of the National Institutes of Health funded "Good Day, Bad Day" research study, and collected information on demographics: age, gender, race; anthropometrics: weight, height, waist circumference. Using a multiplex method (Quansys), plasma cytokines: Interleukin (IL) 1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, IL-23, Interferon gamma (IFNγ), Tumor necrosis factor alpha (TNFα) were measured. Metabolic syndrome (MetSd) was defined according to the Adult Treatment Panel III criteria. Normal values for cytokines were obtained from 93 healthy controls. We used independent sample t test to compare means of continuous variables.

Results:
66 charts of patients with CFS contained available information and pertinent data to complete the analysis of this study. Demographics: age 53±11.5, 85% female, 72.8% non-hispanic white, 18.2% Hispanic, 3% black, 1.5% Asian, and more than 1 ethnicity 4.5%.
MetSd was present in 17 patients (26%), 71% female, 82% white. MetSd was not present in 49 (74%) Cytokine levels were compared between these two groups and no statistical differences were found. Further cytokine level comparison was made between CFS with MetSd and 93 healthy controls, 75% female. Here we found statistically significant differences in IL1α, IL-4, IL-5, IL-6, IL-8, IL-15, IFNγ and TNFα.

Conclusion:
The prevalence of metabolic syndrome in a CFS population was 26%. Plasma cytokine levels in CFS patients with and without co-morbid MetSd were not different.
Similarly to our previously reported findings in CFS, CFS + MetSd patients had abnormalities in proinflamatory, Th2, Th1 and IL-8 when compared to healthy controls.
Affected individuals would be biased towards a T-helper (T_H) 2 type, or humoral immunity-oriented cytokine pattern accompanied by autoantibody production, inappropriate fatigue, myalgia and arthralgia, as well as changes in mood and sleep patterns.
Large longitudinal studies should be performed to determine the contributing factors to this increased risk, and whether the course of metabolic syndrome is altered in this inflammatory state.

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Transient Responsiveness of Inflammatory Cytokines to an Acute Stressor: Comparisons Between CFS and NF

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Objective:
Studies have shown that individuals differ appreciably in their inflammatory responses to acute psychosocial stress, and as cytokines have been implicated in the pathogenesis and clinical manifestations of CFS, we wanted to determine if stress-induced immune-modulation was altered between CFS and non-fatigued controls.

Methods:
Subjects with CFS and matched well controls identified from the general population participated in a 3-day in-hospital study. On the final day, participants were exposed to a standardized psychosocial stressor (the Trier Social Stress Test, TSST), which included free speech and mental arithmetic tasks in front of an audience. Blood was collected at nine time points before, during and after the test. Plasma was assayed for 10 cytokines (IL1b, IL4, IL5, IL6, IL8, IL10, IL12p70, IL15, TNFα and IFNγ) in a multiplexed high-sensitivity assay for the Meso Scale Discovery platform. All analyses was performed on $\log_2$-transformed data to correct for non-normal distributions, and analysis of covariance for repeated measures were performed co-varying for age, sex, race and BMI. Area under the curve (AUCs) for each cytokine was computed using the trapezoidal rule on the raw data and response AUCs were calculated by subtracting baseline from post-baseline AUCs. The data was then log-transformed and used to look at factors such as length of illness, MFI and SF36 scores using Pearson correlation coefficients.

Results:
Significant baseline differences between CFS and NF were noted for IFNγ and IL8, with levels of each being higher in the well controls. Data for IL1b was not included in the analyses as many measures were below the 0.35 pg/ml lower limit of detection. For all cytokines, the TSST elicited a significant increase in cytokine secretion as determined by a paired t-test of each subject's peak level after baseline compared to baseline. All analytes showed a significant change after multiple test correction. Repeated measure MANOVA's were computed for overall TSST differences between CFS cases and well controls (group-effect) which showed differences for IFNg, IL15 and IL6. Differences were seen in response profiles (group by time-effects) for IL15 and IL12p70.

Conclusions:
We show that a psychosocial stressor modulates inflammatory activity. The precise mechanism of this is not known, it could possibly be attributed to the transient mobilization of leukocytes to the periphery caused by sympathetic nervous activation. The mechanism becomes important if we are to understand the differences evident between CFS subjects and well controls in their response to a stressor. The different response profiles between CFS people and NF controls for IL15 and IL12p70 are interesting as IL15 regulates T- and natural killer (NK) cell activation and proliferation, and IL12 plays an important role in the activities of T- and NK-cells. This study attempts to further our understanding of the pathophysiology of CFS using a new paradigm to look at differences between well controls, the application of a stressor and monitoring the response over time.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agency.

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Effects of Alpha1-Proteinase Inhibitor in Peripheral Blood Mononuclear Cells of Chronic Fatigue Syndrome Patients

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Introduction:
Immune dysregulation of 2-5A oligoadenylate synthetase/ribonuclease (RNase) L antiviral pathway has been widely reported in chronic fatigue syndrome (CFS). Proteolytic cleavage of RNase L (83 kDa) by elastase generate hyperactivated low molecular weight forms of RNase L (37 kDa) and ankyrin-like fragments in peripheral blood mononuclear cells (PBMC) of CFS patients. Ankyrin-like RNase L domain might disrupt ABC transporter function, accounting for physiological symptoms of CFS [1]. We hypothesized that alpha1-proteinase inhibitor (A1PI) could inhibit intracellular elastase activity to prevent RNase L proteolytic cleavage in PBMC of CFS.

Objectives:
To demonstrate that A1PI is capable of inhibiting intracellular elastase activity of cultured PBMC from CFS patients.

Methods:
Peripheral blood was drawn from 7 CFS patients fulfilling Fukuda criteria [2] and 5 healthy subjects. Extracts of freshly isolated PBMC were prepared and PBMC cultures were grown in RPMI medium without serum or antibiotics for 12 hours. One third of cultured cells was left untreated and the rest was treated with human plasma-derived A1PI at two different doses (3 g/l and 6 g/l) for 12 hours. After that, cells were harvested to obtain cytoplasmatic extracts. Elastase activity [3] was measured in all samples (mean ± SD).

Results:
PBMC extracts showed mean baseline elastase activity levels of 86±33 U/mg in healthy subjects and 323±106 U/mg in CFS patients. After PBMC culture, a marked increase of intracellular elastase activity was observed in both healthy subjects and CFS patients (up to 757 U/mg and 1503 U/mg, respectively). PBMC cultures in presence of A1PI 3 g/l showed significantly lower intracellular elastase activity, with mean values of 70±14 U/mg in healthy subjects and 132±90 U/mg in CFS patients. Similar results were obtained in presence of A1PI 6 g/l, with mean values of 62±10 U/mg in healthy subjects and 73±18 U/mg in CFS patients.

Conclusion:
In this study it was observed that A1PI strongly inhibited intracellular elastase activity in PBMC of CFS patients. Further research should examine the A1PI effect on proteolytic cleavage of RNase L. Nevertheless, the results indicate that the use human A1PI can be a promising therapeutic agent in the management of CFS.

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T Regulatory Cell Abnormalities in CFS: Another Varying Biomarker is Unveiled That Adds to Understanding of Pathophysiology, Diagnosis and Treatment

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Background:
Deficiency of T regulatory (Treg) cells is now recognized in a number of chronic fatiguing illnesses including Post-Lyme, "mold illness" (chronic inflammatory response syndrome from water-damaged buildings, CIRS-WDB), chronic lymphocytic lymphoma and multiple sclerosis (MS) among many others. Correction of Treg deficiency is associated with clinical benefit. Data from this clinic and others internationally have shown that CFS is marked by absence of neuropeptide (MSH and VIP) control of innate immune inflammatory mediators, especially C4a, MMP9 and TGF beta-1. Successful treatment of affected patients requires correction of these abnormalities, but even with that successful treatment, we noted a subset of patients that remained persistently affected. Because of the known effects of high TGF beta-1 on populations of CD4+CD25+ T reg cells, and in an effort to establish the role of abnormal Treg in CFS, levels in CFS patients were stratified by clinical condition.

Methods:
150 patients in a single practice were identified as controls, untreated cases, treated cases, VIP-treated cases and relapses. CD4+CD25+ levels were measured by flow cytometry by Quest Diagnostics. Patients with symptoms not responsive to standard interventions of reduction of inflammatory markers (N=43) were treated with 50 mcg VIP administered by nasal aerosol QID.

Results**:**
CD4+CD25+ levels in controls were 16.8; untreated cases 6.2; treated cases 17.1; vasoactive intestinal polypeptide (VIP)-treated cases 22.6 and relapses 5.3. Those with the lowest CD4+CD25+ levels were the most symptomatic. Treatment of low CD4+CD25+ with VIP by nasal aerosol led to symptom reduction with rising levels of CD4+CD25+. Use of VIP without correction of underlying innate immune abnormalities did not show significant benefit. In 12 patients, prospective exposure of CFS patients with MSH < 35 pg/ml to WDB with an Environmental Relative Mold Index (ERMI) of > 2 was associated with relapse of symptoms and fall in CD4+CD25+.

Discussion:
Rising levels of TGF beta-1 induces production of CD4+CD25+ regulatory T cells. In inflamed tissue, CD4+CD25+ cells are reported to be altered in situ creating pathogenic T cells which in turn release additional TGF beta-1. Correction of (1) deficiency of CD4+CD25+ cells; and (2) elevated TGF beta-1 result in clinical benefit. Pre-existing CFS is a risk factor for relapse of illness and reduction of Tregs after exposure to WDB.

Conclusions:
Cellular immunity plays an important role in CFS. Reduced levels of Treg cells can be corrected by treatment of inflammatory mediators, with persistent illness responding to use of replacement VIP. CFS patients are at risk for acquisition of additional inflammatory and cellular immune injuries due to exposure to WDB.

Biomarkers in CFS/ME

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Objectives:
Validated laboratory tests are essential for diagnosis and for monitoring therapy of CFS/ME. Diagnosis using the case definition [Fukuda, et al, 1994] requires the exclusion of any other medical explanation for these symptoms, yielding an inefficient, slow, error prone process. This is also costly because the current clinical diagnosis typically involves tertiary care specialists. The search for biomarkers included lymphocyte functions as well as molecules associated with lymphocyte activation, with stress and with inflammation.

Methods:
CFS/ME patients were drawn from the University of Miami (UM) Miller School of Medicine CFS/ME and Immunodeficiency Clinic. All were participants in funded studies (NIH, DOD, Chronic Fatigue Immunodeficiency Syndrome Association (CFIDS) or the Veterans Afairs Merit grant). Prospective biomarkers included natural killer cell cytotoxicity (NKCC), T lymphocyte proliferation in vitro in response to mitogen (LPA), lymphocyte activation markers (CD26, CD38), 16 plasma cytokines and neuropeptide Y. All laboratory evaluations of prospective biomarkers were done in the UM/VA clinical immunology laboratories. The diagnostic accuracy of biomarkers was assessed in terms of true positive (sensitivity) versus true negative (specificity) rates using nonparametric receiver operating characteristics (ROC) curve analyses

Results:
These studies provided credible biomarker status for NKCC, LPA, and markers of lymphocyte activation in CFS/ME. A significant elevation in the relative amounts of 4 of 5 pro-inflammatory cytokines in peripheral blood plasma of patients with CFS/ME was found when compared with the controls Only tumor necrosis factor (TNF)a was unchanged. In cases, lymphotoxin (LT)a was elevated by 257% and IL-6 by 100% over the controls. Both interleukin (IL)-4 and IL-5 were elevated in CFS/ME, with the median of IL-4 240% and of IL-5 95% higher in cases over controls. The anti-inflammatory cytokine IL-13 was significantly lower (15%) in CFS/ME patients while IL-10 was not different. Plasma levels of IL-2 and IFN. in CFS were similar to those in controls. However, IL-12 was significantly elevated (120%) and IL-15 decreased 15% in cases compared to controls. IL-8 (CXCL8) was 42% lower in the CFS/ME patients. IL-17 and IL-23 were not significantly different in CFS cases compared to controls. ROC analyses calculating area under the curve (AUC) for IL-5 (0. 84), LTa (0.77), IL-4 (0.77), IL-12 (0.76) indicated good biomarker potential. The AUC of IL-6 (0.73), IL-15 (0.73), IL-8 (0.69), IL-13 (0.68) IL-1a (0.62), IL-1ß (0.62) showed fair potential as biomarkers. The stress hormone, NPY, was elevated in plasma of CFS/ME cases and positively correlated with perceived stress, anger, depression, negative thoughts and maladaptive coping. ROC analysis indicated that the predictive ability of plasma NPY was significantly better than chance alone in distinguishing patients with CFS/ME from healthy controls.

Conclusions:
Fifteen useful biomarkers were identified in these studies. The differences of these markers in CFS/ME compared to controls also give important information regarding the pathophysiology of the disorder. The association of low LPA response, elevated proportion of activated CD4 and CD8 T cells, defective NKCC, elevated TH2 cytokines with CFS/ME cases suggests that T cells are metabolically limited in performing their helper function. All but one of the inflammatory cytokines measured were elevated as was the stress hormone, NPY – supporting the hypotheses that inflammation and abnormal stress responses are important components in the pathophysiology of CFS/ME.

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Assessment of Natural Killer Cell Receptors in Severe and Moderate Chronic Fatigue Syndrome / Myalgic Encephalomyelitis

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Objective:
A common finding within sufferers of Chronic Fatigue Syndrome (CFS/ME) is abnormalities in the immune system. One of the most consistent findings from a variety of studies to date is that CFS/ME subjects have compromised Natural Killer (NK) cell function. The exact cause of reduced NK function is unknown although there are indications for an involvement in cytolytic proteins. Additionally it is unknown whether decreases NK function is related to NK receptors especially within severely affected CFS/ME patients. Therefore, the purpose of this study is to examine NK phenotypes and lysis as well as receptors within moderate and severely affected CFS/ME subjects in comparison to normal controls.
Method:
Blood samples from 20 normal control participants, 20 moderately affected CFS/ME subjects and 20 severely affected CFS/ME patients. The CFS/ME participants were firstly pre-screened for decreased NK function. Using flow cytometry isolated NK cells were assessed for NK receptor expression and NK phenotypes.

Result:
Preliminary data from CFS/ME patients showed differences within NK cell receptor function when compared to the healthy control group.
Conclusion: Results suggest that NK cell receptor function may be dysfunctional in CFS/ME patients which could potentially explain why these patients have a decrease in NK lysis function.

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The Relationship between Steroid Hormones and Chronic Fatigue Syndrome

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Objective:
Autoimmune diseases are known to affect more females than males. During pregnancy women with autoimmune diseases such as Multiple Sclerosis and Rheumatoid Arthritis tend to experience an improvement in their symptoms. In Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) which may resemble an autoimmune disorder, a similar observation has been made. Currently, there are limited data on the relationship between pregnancy and CFS/ME symptomatology; however, this may be an important clue to understanding the mechanism of CFS/ME. The purpose of this study is to ascertain the role of gestational period in patients diagnosed with CFS/ME.

Method:
The study involves 55 patients diagnosed with CFS/ME based on the Centre for Disease Prevention and Control (CDC). Gene expression analyses using quantitative real time reverse transcriptase polymerase chain reaction (qRT-PCR) and genotyping protocols were used in assessing all PBMC collected from these patients.

Result:
Our preliminary results elucidated differential expression of genes involved in the gestational process in CFS/ME participants. These genes have also been implicated in some aspects of immune function.

Conclusion:
These results suggest a role of the gestational process in the mechanism of CFS/ME. These findings may be important for diagnostic and therapeutic purposes.

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The Effects of Vaccination on Immune Function in Chronic Fatigue Syndrome

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Objective:
Flu like symptoms are a hallmark of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). Additionally, most CFS/ME patients experience severe symptoms of toxin intolerance and hypersensitivity. As CFS/ME is associated with periodoc immune dysfunction, patients may be more susceptible to influenza episodes compared to the normal population. Conversely, their inability to tolerate certain toxins and hypersensitivity responses may affect their immune response to routine vaccines. The purpose of this study is to examine the effects of routine vaccination on immune function in patients with CFS/ME.

Method:
CFS patients were selected based on the Centre for Disease Prevention and Control (CDC) case definition of CFS/ME. A total of 20 CFS/ME patients and 20 health controls were recruited for this study. Blood samples were collected from all participants prior to vaccinations, and 7 and 28 days post vaccinations. Immune parameters that were assessed on the samples included Natural Killer (NK) cytotoxic activity, NK phenotypes, cytokine secretion and the expression of lytic proteins. ANOVA and repeated measures were the statistical methods employed to analyse the data with p-value set to 0.05 as the criterion for significance.

Result:
Preliminary findings suggest a potential role of vaccines in the pathophysiology of CFS/ME.

Conclusion:
These results may be important for developing effective therapies for the management of CFS/ME and establishment of guidelines for immunization of this population.

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Assessment of Natural Killer Cell Function in Chronic Fatigue Syndrome/ME

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Objective:
Immunological abnormalites are recognized as an important components of Chronic Fatigue Syndrome (CFS). Natural Killer (NK) cell dysfunction is the most common immunological finding across studies. It has been suggested that these reductions in NK cell function is caused by decreases in the expression pattern of perforin and granzyme molecules. However, other factors may be involved in NK cell dysfunction.. Hence the purpose of this study is to investigate other potential mechanisms of NK cell dysfunction in CFS/ME.

Methods:
This study examined samples collected from 20 CFS/ME subjects and 5 normal controls. CFS participants were pre-selected by demonstration of low NK cell function and diminished VO_2 max on stress testing. Using flow cytometry and real time quantitative PCR, samples were assessed for levels of cytokines, lytic molecules and expression of miRNAs.

Results:
Preliminary data demonstrated differential expression of cytokines, miRNAs and cytotoxic molecules in the CFS/ME participants compared to healthy controls. Additionally, cytokines, perforin and granzymes were differentially expressed between groups for both the serum and CSF.

Conclusion:
These results confirm the observation of impaired NK cell function in, CFS/ME patients which may be related to alterations in cytokines and lytic proteins.

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ASSESSMENT ISSUES FROM BIOLOGICAL TO BEHAVORIAL

A Chronic Fatigue Syndrome (CFS) Severity Score Questionnaire

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Objective:
Validate a CFS Severity Score based on the 1994 Fukuda criteria in order to have an instrument to compare subject complaints between groups and over time.

Method:
Two Cohorts of CFS, and healthy control (HC) subjects had history and physical examinations to see if they met clinical CFS case designation criteria. Subjects with previous psychiatric, chemotherapy, or chronic illness where fatigue was an element were excluded. After Cohort 1 was examined (n=329), different protocols but the same questionnaire were used with, Cohort 2 (n=212). Subjects scored the severities of the 9 Fukuda criteria for the previous 6 months on a 5 point anchored ordinal scale of: ***No Complaints*** (score=0); ***Trivial*** (1, symptom present but negligible impact); ***Mild*** (2); ***Moderate*** (3); and ***Severe*** (4). Fatigue scores of 3 or 4 defined CFS and chronic idiopathic fatigue (CIF). HC had Fatigue Scores of 0, 1 or 2. The sum of the 8 minor criteria (Sum8) was tested as a surrogate marker of the overall severity of adjunctive complaints. The distributions of Sum8 were explored to see if the 95th percentile (mean+2σ) for non-CFS groups could be used as a threshold to identify CFS subjects.

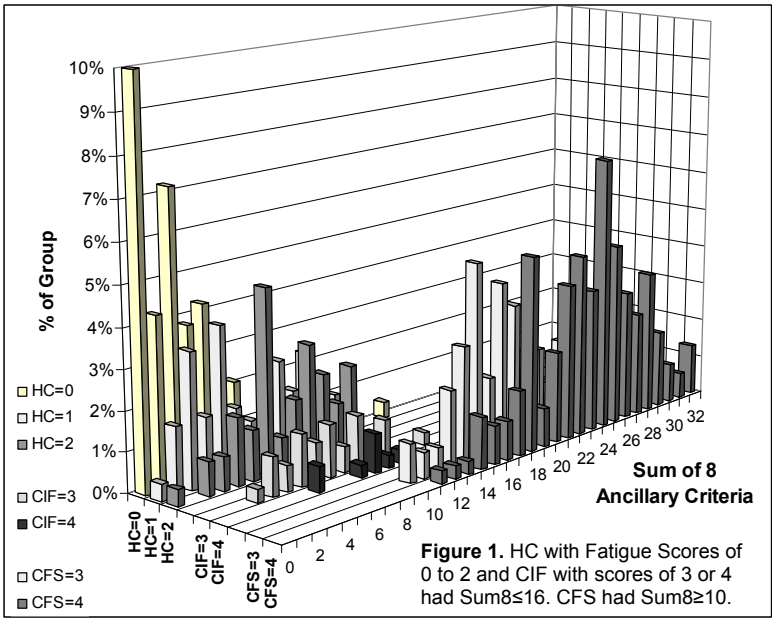

Figure 1. HC with Fatigue Scores of 0 to 2 and CIF with scores of 3 or 4 had Sum8≤16. CFS had Sum8≥10.

Results:
Fatigue Scores of 0, 1 or 2 defined 236 HC (bars on the left). 305 subjects had Fatigue Scores of 3 or 4. Putative CIF (n=36) had ≤ 3 positive minor criteria. CFS with Fatigue Scores of 3 had a mode for Sum8 at 15 to 19; the mode was 24 when 4 was the Fatigue Score. ROC tests found that Sum8=12 had 98.5% for specificity and sensitivity of 97.8% for CFS in this population.

Hierarchical clustering found 4 clades each for CFS and HC. The largest CFS clade (CFS II; n=184) had high severity scores for fatigue, muscle pain, sleep & exertional malaise. The 2nd largest clade (CFS IV, n=51) had lower fatigue, memory, sleep myalgia and exertional malaise scores. CFS clade III (n=30) had fatigue, memory, muscle or joint pain. CFS clade I was an outlier group with fatigue and headache. The largest HC clade (I; n=168, 67% of HC) had low scores for all symptoms. HC II (n=49) had modestly elevated sleep scores (2.4). Myalgia and arthralgia in the mild to moderate range were present in HC III (n=25). HC IV (n=13) had moderate to severe headaches plus sleep and memory problems. These clades of co-existing complaints were highly dissimilar between the CFS and HC groups.

Conclusion:
The CFS Severity Score was robust for discriminating CFS from HC subjects in this population. Mechanisms underlying the clades are under investigation.

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Usefulness of a Joint and Multidisciplinary Unit for the Diagnosis, and Management of Chronic Fatigue Syndrome (CFS), Multiple Chemical Sensitivity (MCS) and Fibromyalgia

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CENTRE SANITARI DEL SOLSONES FUNDACIO PUBLICA I COMARCAL.

We present the structure and functioning of our unit as an example of multidisciplinary and co-management of the central sensitization syndromes.

The Centre Sanitari del Solsonès (CSS) is a public medical center serving the region of Solsonés, an area of Central Catalonia around 15000 inhabitants.

In 2010 we created a unit for the diagnosis and management of the diseases that has an internal medicine physician expert on the three diseases, a nurse, a psychologist and a physiotherapist.

The patient arrives at the unit referred by primary care physicians. The nurse manages and cites the patients for the first medical visit where the doctor takes the patient's medical history. Subsequently, the patient is sent to the nurse who perform the nursing history, assessment tests of fatigue (FT. SF-36), pain (FIQ) and chemical sensitivity (QEESI). The patient is then referred to the psychologist who performed psychological and neurocognitive assessment. Subsequently, clinical meetings are held together for determining the diagnosis, the degree of impairment and the proper course of action. The unit has also a group of cognitive-behavioural treatment involving all the professionals of the same. Diagnosed patients enter the patient registry that records the incidence and prevalence of the three diseases as well as clinical and epidemiological parameters. Currently, and after a year of operation the registry has more than 50 patients.

Conclusion:
We believe that the joint multidisciplinary units that treat the three diseases are the best tool for correct diagnosis, grading, handling and study of this pathologies.

Six Functional Capacities That Impact People with CFS/ME and/or Fibromyalgia

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Objectives:
CFS/ME, fibromyalgia and related chronic illnesses have a significant impact on educational, work, and social success, as well as on activities of daily living, including self care, school, work and socialization. Workplaces, schools, social communities and other systems are challenged to provide appropriate accommodations to help people with chronic illnesses succeed to their highest capacity. A unique challenge is that, because these chronic illnesses relapse and remit, the accommodations must be flexible enough to change along with the person's health status.

Methods:
This presentation will outline the six functions that that are impacted by chronic illness and that affect the patient's participation in work or school. These are: 1. Pain; 2. Fatigue (“tired and wired,” sleepy); 3. Sleep Quality; 4. Mood/Presentation; 5. Cognition/Mental Focus; and 6. Ambulation/Movement.

It will also explain the Fennell Four Phase Model of chronic illness, an empirically validated model that describes four phases of adaptation that occur in chronic illnesses and trauma. These phases -- 1. Crisis; 2. Stabilization; 3. Resolution; 4. Integration -- describe a predictable passage that patients navigate on their way to defining a new self and a new life after the onset of chronic illness.

Results:
Research shows that people with CFS/ME and fibromyalgia pass through Four Phases as they learn to manage and cope with their decreased or impaired function, and the individual's health, functional status and Phase placement impact one another over time.

Conclusion:
By assessing a person's functional status and Phase placement, professionals can implement accommodations that give the patient the highest likelihood of success in the workplace, classroom and other environments.

Relationship to Conference Theme:
By conceptualizing the experiences of people with chronic illnesses with the functional capacity and phase placement concepts, professionals across disciplines can step outside of a medical/clinical framework and describe commonly shared human experiences in a substantive and meaningful manner that supports the individual's success. In addition, patients and families can utilize these functional area and phase placement concepts as a personal insight tool that helps them understand their current abilities and limitations, work within the parameters they are experiencing, and allow them to make better decisions about how to utilize their time, schedule and energy, on any given day.

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Adverse Childhood Experiences as a Risk Factor for Chronic Fatigue Syndrome

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INTRODUCTION:
Chronic Fatigue Syndrome (CFS) is characterized by severe, disabling fatigue and other symptoms, including musculoskeletal pain, sleep disturbance, attentional impairment, and anxiety. Although its etiology is not completely understood, it is considered that it is determined by biological, psychological and social factors. Adverse childhood experiences have been described as one of the major environmental risk factors for CFS.

AIM:
To evaluate the prevalence of different childhood traumas in a sample of adult CFS patients and the contribution of them in CFS symptoms profile.

METHODS:
The initial sample consisted of 142 patients, of whom 9 were excluded because of severe psychopathology or incomplete evaluation. All the patients (age 48±8,9; 92,9% women) received CFS diagnoses according to Fukuda criteria. Childhood traumatic events were assessed by clinical interview in a dichotomous pattern. The scales FIS-40 and HAD were administrated.

RESULTS:
74 (40,4%) patients reported some adverse childhood experience (ACE) [19 (10,4%) physical abuse, 19 (10,4%) sexual abuse, 25 (13,7%) emotional neglect, 27 (14,8%) bulling]. When comparing those with some ACE with those without it, there were no differences in Fukuda criteria profile, FIS-40 (124,47±24,56 vs 124,08±26,26; p=0,94), HAD-Anxiety (10,38±4,95 vs 10,65±5,08; p=0,81) and HAD-Depression (10,54±5,50

Validation of a Neuropsychological Battery in a Sample of Patients with Chronic Fatigue Syndrome

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OBJECTIVES:
Some cognitive deficits have been identified, although the findings are inconsistent and hindered by methodological heterogeneities. One of these limitations is the used neuropsychological battery. Some studies show that cognitive measures that share variance in healthy people can dissociate and contribute to unique variance in people with some cognitive impairment. They suggest that the validity in neuropsychological measures should be tested in homogeneous samples. The aim of this study was to test the validity of a neuropsychological battery in a sample of patients with CFS.
METHODS:
Sixty-eight women, aged between 29 and 67 years-old and diagnosed with CFS according to the criteria of Fukuda were enrolled. We excluded patients with mental disorders (except depression reactive to illness) and organic diseases that can course with cognitive impairment. Patients were assessed with the following neuropsychological test: Mental Control, Paced Auditory Serial Addition Test, Digit Span, Symbol Digit Modalities Test, Stroop Test, Trail-Making Test, verbal fluency test, Tower of London test, Rey Auditory Verbal Learning test, Rey-Osterreith Complex Figure and Grooved pegboard. Twenty-five cognitive measures were obtained. Because the multidimensionality of the cognitive functions studied, principal components analyses including all the measures were carried in order to assure that each one was comprised of only one cognitive dimension.

RESULTS:
The neuropsychological measures were categorized into 7 specific cognitive domains: Attention/concentration, divided attention, verbal memory, visual memory, executive functioning, problem solving and motor functioning. The Cronbach´s alpha for all analyses was upper than .05.

CONCLUSION:
This study proposes a validation of a neuropsychological battery in a homogeneous sample of CFS. This proposition could reduce one of the main limitations in the studies about CFS and cognitive functioning, such as the inconsistent findings associated to the different neuropsychological test used.

Easy Monitoring of the Th1/Th2 Balance Status in Health and Disease with Special Emphasis on CFS/ME

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Objective:
It is generally agreed that CFS/ME is a Th2 shifted condition. However, simple self-tests allowing physicians and CFS/ME patients to follow-up on Th1/Th2 balance during therapy are lacking and therefore it still remains very difficult for an individual to evaluate whether the treatment he or she is undergoing is really effective. In addition, the effectiveness of over the counter sold products claiming to balance Th1/Th2 status such as anti-oxidants, pro-biotics and other should be evaluable on a personal basis. A lot of CFS/ME patients are trying to improve their condition by exploring so-called neutraceuticals by “trial and error” without realizing the potential risk of further deterioration of their health by randomly taking products that may even further disturb their Th1/Th2 balance. Therefore we developed a simple “self-test” principle allowing patients to determine their Th1/Th2 profile over short periods of time and to follow-up on the effect of therapy and intake of drugs and neutraceuticals or any other strategy to balance Th1/Th2 status.

Methods:
By analyzing a massive number of first morning urine samples obtained from patients facing conditions associated with an overactive Th2 arm (ulcerative colitis, autism, blastocystis, mercury poisoning, viral infection) we came across a reaction principle that uses a colorimetric substrate changing color upon reaction with metabolites contained in the urine samples from yellow (neutral) over light green and brown (moderate Th2) to deep purple and black (strongly Th2 shifted). The development of the color is time-dependent and quantitative.

Results:
More than 80% of urine samples obtained from CFS/ME patients produced a time-dependent quantitative change in color compared to 4% of the controls (perfectly healthy population).
Conclusion: The urine test principle we’ve developed offers an easy way to determine and to follow-up on Th1/Th2 balance in health and disease and more in particular at the same time provides further evidence that CFS/ME is a condition merely associated with an overactive Th2 arm.

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ROLE OF CELLULAR PRION PROTEINS (PrPc) IN CFS/ME AND OTHER CHRONIC DISEASES

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Objective:
Cellular prion proteins (PrPc) are small glycoproteins attached to the outer leaflet of the plasmamembrane of mammalian cells by a glycosylphosphatidyl anchor. The isoform of the prion protein is expressed in hematopoietic stem cells, neuronal cells, T and B lymphocytes, natural killer cells, muscle, intestinal tract, spleen, adrenal glands, endothelial cells, platelets. PrPc binds copper, plays a role in calcium uptake, protects cells against oxidative stress, prevents cells from apoptosis, interacts with viruses (binds gp-120), is involved in neuroprotection and plays an important role in immune and angiogenic responses. Therefore we estimated that hallmarks of CFS/ME such as oxidative stress, calcium channelopathy, T-cell dysfunction, copper uptake changes, altered red blood cells and oxygen transport, coagulation and hormonal responses (HPA-axis) as well as viral entry could be attributed to aberrant PrPc function which could than ultimately explain the "multi-system" character of the CFS/ME disorder. In order to investigate PrPc function in CFS/ME, we first needed to develop a test allowing to measure "activity" of PrPc in "real time".

Methods:
We have developed a cell-based chemiluminometric (CL) assay accordingly to the following principle: cells or tissue under study are incubated in an appropriate buffer in the presence of a chemiluminometric probe (CLP). Next a PrPc redox-trigger is added that stimulates PrPc-mediated reactive oxygen species (ROS) production which is proportional to the active state of the PrPc and which ROS react with CLP to produce a basal glow of light (Lb) that can be detected in front of a photomultiplier. Next, to an identical sample and CLP an additional trigger is added that stimulates cells to produce ROS at maximum capacity, producing maximum glow type chemiluminescence (Lmax). Lmax/Lb defines a PrPc functional stimulation index (SI) that can be compared for different tissues and cells obtained from controls and patient populations.

Results:
Peripheral blood mononuclear cells (PBMC's) obtained from CFS/ME patients show aberrant SI's (extremely low SI<3 or extremely high SI>20 compared to controls (SI=10 +/- 3). In addition we could demonstrate the influence of heparin, minocyclin, metals (copper, mercury) and other agents on PrPc function by means of this luminometric technique

Conclusion:
PrPc functionality of PBMC's is altered in CFS/ME. Chemiluminometric analysis provides a useful tool to further develop and explore PrPc functional tests and PrPc drug interaction platforms (drug discovery) in CFS/ME and other chronic diseases (fibromyalgia, rheumatoid arthritis, autism, cancer).

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Live, Moving Varestrongylus klapowi: an Atypical, Chronic Nematode Parasite in the Nasal Washings of CFS Patients

Lawrence A, Klapow, PhD*,
Neil Nathan, MD **

Objectives:
- Obtain "proof of life" evidence for the atypical *V. klapowi* (Vk) parasite by documenting the vital movements of living worms.
- Develop a rapid accurate method for diagnosing the infection by analyzing washings from nasal membranes.
- Determine the ethanol concentration for effective nasal spray disinfectants.

Methods:
A nasal irrigation bottle was used to force warm physiological saline (0.9% NaCl, ~90°F) up one nostril to collect fluid (~60 ml) through the other nostril of CFS patients who were previously shown to be positive for the Vk parasite by sputum analysis. Vk specimens were allowed to settle to the bottom of a 50 ml test-tube suspended in warm water (~90°F), gently pipetted to a warm dish and video-graphed under a stereo-microscope. Moving worms were also video-graphed using intense halogen lighting on a compound microscope equipped with two polarizers (one in the illumination, the other in the image path) to reduce glare. Four Vk positive patients previously diagnosed by sputum analysis (inhalation of 1% ethanol for 30 minutes, then self induce coughing) were re-tested by the nasal washing method. Two patients inhaled the fumes of 40% ethanol through the nose for 10 breaths just prior to the nasal washing which my have helped release live worms.

Results:
Video-graphs showed gross body locomotion as well as rhythmic movements of internal organs. Repeated thrusting movements of the head were seen in the tissue boring fourth stage larva. Whole body contractions were seen in males. Rapid repeated rhythmic contractions of the digestive track (esophagus and intestine) and associated glands were seen in these and other stages. All four patients who were positive by sputum analysis were also positive by the nasal washing method. Previous experiments had shown that inhalation of one percent nebulized ethanol for 30 minutes sterilized sputum from the lungs. Higher concentrations, currently being studied, will likely achieve more rapid sterilization of nasal membranes.

Conclusions:
Varestrongylus klapowi is an anatomically specialized nematode, not an artifact, as evidenced by the vital movements of live specimens showing both gross locomotion and rhythmic movements of internal organs. It has recently been isolated from nasal washings of CFS patients who were previously positive by sputum analysis. The infections are chronic and widely disseminated as they occur in the same individuals over many years, in sputum, intestinal, and now, nasal washings. A study using the nasal washing method is being planned which will attempt to confirm previously reported, statistically significant, blinded sputum analysis linking the infection to CFS. Dilute ethanol sprays can kill the Vk parasite on mucus membranes.

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Chronic Rhinosinusitis as an Overlooked Chronic Fatigue Syndrome Exclusionary Condition

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Objectives:
To search for symptom similarities between chronic rhinosinusitis (CRS), a chronic fatiguing illness, and unexplained chronic fatigue (UCF).

Methods:
A MEDLINE literature search of the symptoms and natural history of CRS was performed.

Results:
Fatigue is one of eight symptom criteria formulated by the American Academy of Otolaryngology–Head and Neck Surgery Rhinosinusitis Task Force to establish the diagnosis of CRS. Chronic rhinosinusitis–related fatigue is associated with symptom severity scores approximating those of other CRS-related symptoms, including facial pressure, headache, and nasal discharge. In one series of patients with CRS, 86% of those surveyed noted fatigue, which was described as severe or very severe in 32% of patients surveyed and as the most disabling CRS symptom in 14% of patients surveyed.

In the only meta-analysis comparing CRS vitality scores on the 36-Item Short Form Health Survey (SF-36) before and after sinus surgery, all preoperative vitality scores were below local norms. In the only series comparing CRS vitality scores with other disease norms, vitality scores were significantly lower (worse) than those of patients with congestive heart failure, chronic obstructive pulmonary disease, or chronic back pain.

Fatigue associated with CRS improves after sinus surgery. Patients with CRS and severe fatigue demonstrate greater improvement in fatigue than the improvement noted in patients with less severe fatigue after surgery. Similarly, patients with CRS and concurrent fibromyalgia demonstrate greater improvement in fatigue than the fatigue improvement noted in patients without fibromyalgia.

In a study of patients with UCF, CRS symptoms were significantly more common than in patients without UCF. Odds ratios (95% confidence intervals) for CRS symptoms in that study were 9.7 (5.2-18.2) for facial pressure, 21.9 (10.9-44.0) for heavy-headedness, 3.1 (1.5-6.6) for sore throat, and 9.2 (4.3-19.7) for tender cervical lymph nodes.

In a meta-analysis comparing CRS bodily pain scores on the SF-36 before and after sinus surgery, all preoperative bodily pain scores were below (worse than) local norms. Bodily pain associated with CRS improves after sinus surgery.

Chronic rhinosinusitis usually begins with a significant upper respiratory tract infection, as is often observed with UCF. All UCF symptom criteria have been documented in CRS. Like UCF, CRS is not associated with objective findings. In patients with CRS, no abnormalities are noted on routine or specialized blood tests. Although sinus computed tomographic (CT) images can document sinusitis, symptoms usually do not correlate with CT findings, and the extent of abnormalities noted is often similar in patients with and without CRS symptoms.
Conclusions:
Chronic rhinosinusitis is a fatiguing illness usually unassociated with objective findings and defined by symptoms similar to those of UCF. Therefore, CRS should be considered a possible cause of otherwise unexplained fatigue and should be studied for atypical mechanisms that cause fatigue. In addition, CRS, a treatable illness, may easily be misdiagnosed as UCF.

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Prefential Pathway Activation in Gulf War Veterans with Unexplained Neuroendocrine-Immune Imbalances

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Objectives:
Though potentially linked to the basic physiology of stress response we still have no clear understanding of Gulf War Illness (GWI). Indeed clinical presentation of GWI overlaps strongly with that of another stress-mediated illness: Chronic Fatigue Syndrome (CFS). Recent efforts by our group have cast individual molecular messages in the greater context of immune signaling and cellular demographics. Here, we extend this approach by incorporating *a priori* knowledge of biological pathways to support molecular discrimination of these sister illnesses.

Methods:
Cohort. Male CFS (n=7), GWI (n=20) and healthy veterans (n=11), comparable in age, body mass index (BMI) and ethnicity, were assessed using Fukuda criteria. Stress response was stimulated by way of a standard Graded eXercise Test (GXT) and blood drawn 30 minutes prior to exercise, at peak effort (VO2 max) and 4-hours post exercise while controlling for diurnal variation. Gene expression in circulating immune cells was measured using the Affymetrix HG U133 plus 2.0 microarray. *Computation*. Using a novel method we first assessed compatibility in the expression of genes supporting a pathway segment with the expected molecular association dictated by known biochemistry. For pathway segments supported consistently in the data we then estimated the likelihood that these step reactions were active in a specific sample. Pathway segment activity levels were computed in every sample in the response time course and then compared across patient groups using standard non-parametric tests.

Results:
Even at rest CFS and GWI patients were distinguished from each other and from controls with an accuracy of >85% with fewer than 3 pathways. Using progression across all 3 time points, single pathways were sufficient to separate groups. CFS and control subjects were distinguished with 85% accuracy by suppression of *alanine and aspartate metabolism* (KEGG) alone ($p_{Wilcoxon}<0.0001$). Similarly a classification accuracy of close to 80% was obtained for GWI subjects on the basis of activity in the *1- and 2-methylnaphthalene degradation* pathway (KEGG) ($p_{Wilcoxon}=0.05$), which appeared chronically suppressed in this group. Finally, CFS and GWI subjects were best distinguished with activity in *chondroitin sulfate biosynthesis* (KEGG) (accuracy >85%; $p_{Wilcoxon}<0.0001$). Complete separation of these illness groups was achieved with the addition of *aurora A signaling* (NCI/Nature) ($p_{Wilcoxon}<0.0001$) and signaling mediated by transmembrane protein *syndecan-1* (NCI/Nature) ($p_{Wilcoxon}=0.024$). Aurora A activity is a key component in mitosis and meiosis. It has been associated with a range of malignancies and is significantly increased in GWI vs. CFS. Conversely syndecan-1 has been used as a marker of effector B cell activity and is significantly depressed in GWI compared to CFS patients.

Conclusion:
Together these pathway segments supporting immune signaling, cytotoxic function and metabolism offer not only a framework for molecular diagnosis but also a glimpse into fundamental imbalances in immune cell signaling and metabolism in each illness.

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ME/CFS and Bullying in Context of Social Interactions

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PhD Candidate
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Objectives:
To examine the nature and impact of bullying of persons with ME/CFS when engaged in an institutional encounter.

Method:
The initial phase of the research involved a thorough review of the available literature to establish the interaction of those with ME/CFS with social institutions. A focus for this paper was made on the incidence of bullying behaviour that participants reported as having experienced during such interactions and attention was paid to the consequences of such experiences. In the data collection phase, a pilot study involving an investigation of the Australian perspective of the experience of ME/CFS was obtained. This was expanded in the main study and participants were provided the opportunity to reveal their stories. Participants were required to have a diagnosis of CFS, ME or ME/CFS from a medical practitioner and self-select themselves as compliant to the Fukuda CFS Criteria, Canadian ME/CFS Criteria and Ramsay ME Criteria.

A background questionnaire was provided to give an insight into the history of the participant, particularly interactions with social institutions and pathways to diagnosis. The interview drew upon the questionnaire for guidance, with the primary questions derived from information gained from the literature review. The interviews were transcribed, coded and the relationships and issues identified in order to guide the second phase of the research which was conducted further into the study.

The pilot study involved 3 participants, followed by a second, more comprehensive phase comprising 16 participants. Stories emerged from within those interviews with respect to interactions with society and these were broken down to reveal particular themes relevant to those experiences.

Results:
A total of 19 interviews were conducted. The average age of participants was 91.95 with all 14 females and 5 male participants. The mean duration of the condition was 17.66 years, with 8.35 years from onset until diagnosis. A number of issues arose, revealing an insight into the nature of the relationships that exist between persons with ME/CFS and various social institutions. Relationships of power, politics, policies, practices and social relations were revealed to play an important role in the experience of ME/CFS. Bullying appeared to occur across every facet of the participant's lives, particularly in dealings with the medical profession,

insurance companies, educators, employment, family, friends and the media. Whilst apparently present such behaviour was not named as such nor addressed.

Conclusion:
Persons with ME/CFS are subject to bullying directly or indirectly because of their diagnosis and the contested nature of the condition. This experience has an adverse impact upon the person – both physically and emotionally. Patients reveal that such encounters can influence their dealings with people within social institutions and impact adversely upon their condition and manner in which they address future interactions. Rarely is bullying identified, nor is action taken against the perpetrators. Knowledge of steps to be taken and inability to pursue action against perpetrators due to illness prevented protection of rights and self. Providing a more settled understanding of the condition and education within society is indicated as a counter measure to identify and prevent the incidence of bullying.

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ME/CFS: First Do No Harm

Geoffrey Hallmann
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Objectives:
To examine the nature and impact of the medical encounter by persons with ME/CFS.

Method:
The initial phase of the research involved a thorough review of the available literature to establish the interaction of those with ME/CFS with social institutions. A focus for this paper was made on the interactions between doctors and medical staff with persons with ME/CFS to establish the current evidence. In the data collection phase, a pilot study involving an investigation of the Australian perspective of the experience of ME/CFS was obtained. This was expanded in the main study and participants were provided the opportunity to reveal their stories. Participants were required to have a diagnosis of CFS, ME or ME/CFS from a medical practitioner and self-select themselves as compliant to the Fukuda CFS Criteria, Canadian ME/CFS Criteria and Ramsay ME Criteria.

A background questionnaire was provided to give an insight into the history of the participant, particularly interactions with social institutions and pathways to diagnosis. The interview drew upon the questionnaire for guidance, with the primary questions derived from information gained from the literature review. The interviews were transcribed, coded and the relationships and issues identified in order to guide the second phase of the research which was conducted further into the study.

The pilot study involved 3 participants, followed by a second, more comprehensive phase comprising 16 participants. Stories emerged from within those interviews with respect to interactions with the medical community and these were broken down to reveal particular themes relevant to those experiences.

Results:
A total of 19 interviews were conducted. The average age of participants was 91.95 with all 14 females and 5 male participants. The mean duration of the condition was 17.66 years, with 8.35 years from onset until diagnosis. A number of issues arose, revealing an insight into the nature of the relationships that exist between persons with ME/CFS and medical staff. Relationships of power, politics, policies, practices and social relations were revealed to play an important role in the experience of ME/CFS. Positive and negative experiences revealed issues relating to belief, awareness, education, research, school of thought, attitude, investigation, historical analysis, guidelines, personal experience, finances, and politics. Thematically the participants identified empathy, knowledge, and management as attributes that pointed towards what patients consider to be best practice when dealing with medical practitioners. The stories provide a significant insight into the various medical personnel and medical settings that participants have encountered and how that interaction impacted upon their perceptions and the status of their condition.

Conclusion:
The relationship between persons with ME/CFS and medical staff, particularly doctors is very important to the progress of the patient. The experiences reveal the importance of knowledge, empathy and management to the patient-doctor relationship. Poor experiences have led patients to adverse reactions within their condition and led them look to alternative therapies due to a lack of faith in the medical profession. Beliefs, knowledge and understanding of their condition also had bearing upon the experience.

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Objective Biomarkers For The Fatigue State -The Changes Of Oxidation Stress-

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Background:
It is well known that the accurate evaluation of fatigue states in each subject is quite difficult, because the levels of fatigue depend on the subjective feeling. Since 2009, the study group (head: Hirohiko Kuratsune) supported by Japanese Ministry of Health, Labor and Welfare has been working for the establishment of objective biomarkers to diagnose the fatigue states in Japan. We present here the relationship between the fatigue states and the changes of oxidation stress.

Materials and Methods:
To investigate the role of oxidative stress in the pathogenesis of fatigue states, we measured both oxidation and anti-oxidation activities simultaneously in sera from 303 patients with chronic fatigue syndrome (CFS), 24 people with severe industrial fatigue, 20 healthy students before and after 3 hour mental workload and 312 healthy volunteers by using the d-ROMs test and the BAP test (Diacron; Grosseto, Italy). The oxidation stress index (OSI) was calculated by the following formula: OSI = (d-ROMs / BMP) × 8·85 (a coefficient for standardization to set the mean of healthy individuals to 1.0).

Results:
The oxidation activities (d-ROMs) in 312 healthy controls are 286.9 ± 50.1 unit (mean ± SD), and the d-ROMs are related to their age. The d-ROMs are higher in female than in male. On the other hand, the anti-oxidation activities (BAP) in 312 healthy volunteers are 2541 ± 60.8 μmol/L, and the BAP are not related to the age and sex. In the CFS group, the d-ROMs and the BAP are 328.8 ± 81.3 units and 2508 ± 102.6 μmol/L, respectively. The d-ROMs are significantly higher in the CFS group than in the control group ($p<0.001$), and the BAP are significantly lower in the CFS group than in the control group ($p<0.001$). The OSI are related to the Performance Status in the CFS patients ($p<0.005$). In the severe industrial fatigue group, the d-ROMs are 410.0 ± 67.0 units, and they are significantly higher in the severe industrial fatigue group than in the control group ($p<0.001$). The BAP are 2527 ± 115.5 μmol/L, and there is no significant difference in the BAP between the severe industrial fatigue group and the control group. When we studied the d-ROMs and the BAP before and after 3 hour mental workload in 20 healthy students, the d-ROMs and the BAP are 301.3 ± 23.6 unit and 2389.6 ± 81.2 μmol/L before workload, and 321.2 ± 33.0 unit and 2438.8 ± 92.9 μmol/L after workload, respectively. After mental workload, both the d-ROMs and the BAP are significantly increased as compared to those before mental workload, and there is no difference in the OSI between before and after workload.

Conclusion:
The evaluation of oxidation and anti-oxidation activities by using the d-ROMs test and the BAP test reflects not only the clinical condition with or without fatigue state, but also the etiology of fatigue state. Therefore, these evaluations might make useful objective markers for diagnostic evaluation of fatigue states.

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Nagalase Activity is Inversely Correlated with CFS Clinical Status (KPS)

Paul R. Cheney MD, PhD

Introduction:
The sera of patients with HIV and cancer possess alpha-N-acetylgalatosidase enzyme activity known as Nagalase activity. This glycosidase activity appears to reside in the proteolytically cleaved gp160 envelope protein of HIV and also found in the similarly cleaved envelope protein of influenza virus and possibly possessed by other classes of virus that probably induces viral virulence as this glycosidase activity appears to be important in both cellular entry by virus-to-membrane fusion and immunosuppression. Nagalase activity specifically destroys the Gc protein (VDBP) precursor capacity for GcMAF activity leading to direct immunosuppression. Cancer cells also secret Nagalase activity that may come from genomic activation of HERV's within these cells or other viruses active within such cancer cells. In metastatic breast cancer, Nagalase activity correlates with tumor burden and Nagalase values dropping to control ranges near zero correlate with eradication of tumor cells resulting in a prolonged cancer free state lasting years. Nagalase has also correlated even better than CD4 counts for clinical status of HIV patients.

Methods:
We measured Nagalase activity in 50 consecutive CFS cases with an average age of 47.7 years. There were 20 males and 30 females from a national CFS referral center meeting the 1994 CDC CFS case definition. Serum Nagalase activity was measured in nmoles/min/mg protein by a commercial laboratory (ELN Labs, NJ). The idea to measure Nagalase was suggested by the detection of XMRV in the great majority of patients in this national practice (> 75% positive for XMRV with one measurement and > 95% if measured more than once at a CLIA certified laboratory, VIP Dx, NV). All patients during their office visits at this clinic are routinely given a physician assigned functional capacity score known as the Karnofsky Performance Score or KPS which has been well validated in both CFS and other chronic diseases. This clinic has had two decades of experience using this physician applied functional score including FDA sponsored clinical trials. Patients were sent kits for Nagalase testing and then assigned a KPS score in their charts. Inter-assay measures of KPS typically can vary plus or minus 5 KPS units over time by chance alone in CFS unless there is a significant shift in clinical status which usually occurs slowly over time. KPS is not a symptom score and expresses what the patient can and cannot do with respect to activities of daily living.

Results:
The Nagalase activity of 50 consecutive CFS cases reported here averaged 3.0 nmoles/min/mg protein, range 0.8 – 6.7. The Nagalase mean of CFS cases is comparable to HIV and comparable to breast cancer in respect to both mean and range. Average KPS was 59, range 40-90. Correlation statistics were developed for Nagalase vs. KPS. KPS was found to be negatively correlated with an r-square of 0.3, $p < 0.00005$, $N = 50$. The only two CFS cases with a KPS > 80 were at control values for Nagalase and one was our best responder to GcMAF (see GcMAF Abstract). XMRV detection rate in this 50 patient cohort was 77%, mostly single measures by culture and/or serology.

Conclusion:
Nagalase activity has been previously demonstrated to be an excellent clinical status marker in HIV and cancer. This data supports the hypothesis that Nagalase activity is also a good clinical status marker for CFS. The origin of Nagalase activity in CFS remains unknown but its finding in all disabled cases to date and that it correlates with clinical status along with the finding that almost all of the same cases are XMRV positive supports the hypothesis that XMRV may be the cause or contributes to Nagalase activity in CFS.

To Show How the Propensity for Chronic Fatigue Is Set Up During Infancy and Childhood

Kim Knight, Mickel Therapist

Objectives:
To show how the seeds and propensity for chronic fatigue and related syndromes are sown during infancy and childhood via the mental patterning and emotional conditioning set in place in the environment. So-said patterns and conditions result in the formation of limiting self-beliefs and ensuing disempowering behaviours which put the body into an abnormal and perpetual state of stress. This eventually rewires the cells into illness.

Methods:
By taking a detailed case history from birth to the present with more than 500 clients and noting in particular the mental and emotional perceptions or responses to upsetting and traumatic events.

Results:
In every case, without fail, unconscious negative and self-limiting beliefs were set up in childhood which in turn led to disempowering behaviours towards self. This put the body into a perpetual state of stress (sympathetic response) from a very early age which over time resulted in physical depletion such as adrenal exhaustion and a weakened immune system which opened itself up to viruses. This in turn eventually led to chronic fatigue.

Conclusion:
The propensity for chronic fatigue is set up in childhood via environmental factors, in particular mental belief systems and emotional patterns which lead the client to perpetuate life-depleting behaviours which result in illness. Therefore it is essential when looking for solutions to take into account the person's current and past history in its totality. The ongoing evidence can then be used again in practice.

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Effort Perception in Chronic Fatigue Syndrome Is Not Impaired

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Background and Objectives:
Activity pacing is one cornerstone of rehabilitation management for CFS. Optimal criteria for pacing are currently unclear, because patients with CFS may have an impaired ability to self-assess their level of physical exertion. However, this hypothesis has yet to be directly tested. The purpose of this study was to determine the association between subjective and objective indicators of physical effort in patients with CFS and matched controls.

Materials and Methods:
Sixteen patients with CFS and 14 age- and sex-matched non-disabled, sedentary individuals were tested. Each subject received 2 maximal cardiopulmonary exercise tests (CPETs) on a braked bicycle ergometer that were administered 24 hours apart. Heart rate (HR) was measured continuously and rating of perceived exertion (RPE) was assessed at each minute from rest and unloaded cycling until peak exercise. Descriptive statistics (mean ± standard deviation) were calculated for all dependent variables (DVs), including peak HR (HRpeak), HR at VT (HRVT), peak RPE (RPEpeak) and RPE at VT (RPVT). 2x2 analysis of variance (ANOVA) was used to assess the main and interaction effects of group and test on DV measurements. Repeated measures ANOVA was used to assess group and time main and interaction effects on DV measurements. Pearson's correlations (r) were calculated to determine the within-groups associations between HR and RPE during each CPET. Criterion for statistical significance of differences was $\alpha \leq .05$.

Results:
All subjects met standard criteria for maximal effort during each CPET. HRpeak was significantly lower for patients with CFS (CPET1: 158±15 beats per minute [bpm]; CPET2: 156±17bpm) compared to controls (CPET1: 182±13bpm; CPET2: 183±11bpm) on both CPETs ($p<.01$). HRVT also was significantly lower for patients with CFS (CPET1: 113±21bpm; CPET2: 111±14bpm) compared to controls (CPET1: 122±15bpm; CPET2: 131±17bpm) on both CPETs ($p<.01$). RPEpeak was significantly greater in patients with CFS (CPET1: 19.4±1.0; CPET2: 19.6±0.07) compared to controls (CPET1: 19.4±0.8; CPET2: 18.7±2.1) on both CPETs ($p<.01$). RPEVT also was

significantly greater patients with CFS (CPET1: 13.2±2.5; CPET2: 12.7±2.6) compared to controls (CPET1: 10.2±2.5; CPET2: 11.2±2.4) on both CPETs (p<.01). Time series analysis revealed significant group effects for HR (p<.01) and significant group and group x time effects for RPE (p<.01). HR and RPE demonstrated moderate to high correlation in subjects with CFS (CPET1: r=.769, r2=.591; p<.001; CPET2: r=.765, r2=.591; p<.001) and control subjects (CPET1: r=.742, r2=.551; p<.001; CPET2: r=.688, r2=.473; p<.001).

Conclusion:
Subjects with CFS demonstrated significantly greater effort ratings than control subjects during each CPET. HR and RPE were significantly correlated in subjects with CFS and matched control subjects.

Clinical Relevance:
The significant association between HR and RPE indicates patients with CFS can accurately perceive their level of physical exertion. Thus, patients' perceptions of physical exertion can be used with confidence as a basis for pacing self-management programs.

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ME/CFS: Harsh Realities of the Real World

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Objectives:
To conduct a preliminary examination of the experiences of persons with ME/CFS when dealing with society and the social institutions that form the fabric of day to day interactions.

Method:
The initial phase of the research involved a thorough review of the available literature to establish the interaction of those with ME/CFS with social institutions. A focus for this paper was made on the experiences of dealing with social institutions on a daily basis when the diagnosis was known. In the data collection phase, a pilot study involving an investigation of the Australian perspective of the experience of ME/CFS was obtained. This was expanded in the main study and participants were provided the opportunity to reveal their stories. Participants were required to have a diagnosis of CFS, ME or ME/CFS from a medical practitioner and self-select themselves as compliant to the Fukuda CFS Criteria, Canadian ME/CFS Criteria and Ramsay ME Criteria.

A background questionnaire was provided to give an insight into the history of the participant, particularly interactions with social institutions and pathways to diagnosis. The interview drew upon the questionnaire for guidance, with the primary questions derived from information gained from the literature review. The interviews were transcribed, coded and the relationships and issues identified in order to guide the second phase of the research which was conducted further into the study.

The pilot study involved 3 participants, followed by a second, more comprehensive phase comprising 16 participants. Stories emerged from within those interviews with respect to interactions with society and these were broken down to reveal particular themes relevant to those experiences.

Results:
A total of 19 interviews were conducted. The average age of participants was 91.95 with all 14 females and 5 male participants. The mean duration of the condition was 17.66 years, with 8.35 years from onset until diagnosis. A number of issues arose, revealing an insight into the nature of the relationships that exist between persons with ME/CFS and various social institutions. Relationships of power, politics, policies, practices and social relations were revealed to play an important role in the experience of ME/CFS. Positive and negative experiences arose. The contested nature of the condition, its invisibility, lack of community awareness, lack of education, misrepresentation in the media, name, vulnerability of those affected, lack of evidence, barriers to justice and limited support systems all play a role in the way those with the condition experience the social world.

Conclusion:
Persons with ME/CFS are faced with major difficulties when they deal with social institutions. The various factors that play a role in the absence of knowledge and understanding the condition have perpetuated misconceptions within the community. This experience has an adverse impact upon the person – physically, emotionally and financially. Patients reveal that such encounters can influence their dealings with society and can impact adversely upon their condition. Whilst there are mechanisms that can address issues that arise during their life, there exist barriers that prevent protection of rights, access to appropriate investigation, management and care, and little assistance for day to day issues.

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PEDIATRICS

Audit of Paediatric Chronic Fatigue Syndrome (CFS/ME) specialist service in Alder Hey Children's NHS Foundation Trust

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Background:
Alder Hey Children's NHS Foundation Trust is a teaching hospital in the North West of England. The Paediatric Multidisciplinary (MDT) CFS/ME specialist service was established in 2003 as part of the Department of Health initiative on developing services specifically for children of all ages with CFS/ME. The MDT team included Consultant Paediatrician as the lead, CFS/ME specialist nurse, senior physiotherapist, psychologist, consultant psychiatrist and a medical secretary. There were 91 children managed by this service in weekly dedicated CFS/ME MDT clinics by early 2008. This service was delivered based on the already existing guidance from the Chief Medical Officers report, National Service Framework for children, General Medical Council's good medical practice and the RCPCH publication. However in 2007 the National Institute of Clinical Excellence (NICE) published specific evidence based guidelines on the management of adults and children with CFS/ME (CG53) which is being actively followed now.

Objectives:
The objective of this audit was to review the standard of our care towards children and young people with CFS/ME based on the NICE guidelines CG53.

Methods:
This was a retrospective case notes audit of 50 children seen by our CFS/ME service between December 2003 and July 2008. The lead clinician completed the audit with the help from the Hospital audit committee.

Results:
There were 40 female and 10 male children with CFS/ME. The mean age of our study population was 12.3 years (range 7-16 years). 60% of the children were referred by other paediatricians. In 96% of the study population the symptoms persisted for more than 3 months. 62% had missed school at some time during their illness. The diagnosis was established by the MDT team in 42/50 and by other paediatrician in 6/50. Appropriate investigations were undertaken, other underlying diagnosis excluded, child and family focussed treatment plans initiated and additional information on the illness and support was provided to all patients as suggested by the CG53. However only in 93% of patients early symptom advice was provided. The mean duration from referral to the time seen in clinic was 7.4 weeks. Only 49% were seen within 6 weeks of referral as suggested by the CG53. All but one patient were managed as outpatients by the specialist team.

Conclusion:
Review of clinical care based on established evidence based standards has helped us in identifying areas for improvement and deliver high quality service to our children with CFS/ME. This could be used as a regular exercise on a regular basis.

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Patient and Parent Survey in a Specialist Paediatric Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) Service in Alder Hey Children's NHS Foundation Trust

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Background:
In the last 2 decades there is an increasing awareness and recognition of CFS/ME in children. The National Health Service in UK has established several specialist CFS/ME centres across the country to treat children with this severe debilitating illness. Unfortunately not all are able to access these services. Even if they access the quality of service delivery is variable. This is primarily due to inequality in service provision, lack of understanding of the aetiology of this condition and varied clinical knowledge and expertise of the clinical teams. In Alder Hey following the Department of Health initiative a local Multi Disciplinary Team (MDT) specialist service was set up in 2003. The team consisted of a consultant paediatrician, specialist nurse, physiotherapist, psychologist and a consultant psychiatrist. As it was relatively new area of practice it was believed that there were lot more to listen and learn from the children and their families how a high quality service could be delivered. Hence in 2008 patient and parent experiences survey was undertaken.

Aim:
To obtain qualitative information on patients and parents experiences of the CFS/ME service

Methods:
The Commission for Healthcare Improvement (currently the Care Quality Commission) questionnaire was given to all families who attended the weekly clinics between February and April 2008. They were completed both by the child and the parent. The completed questionnaires were posted in a box to ensure confidentiality. The results were analysed by the audit department.

Results:
There were 52 children actively being managed at that time. The questionnaires were given to 25 families. 25 (48%) of patient population and 24 (46%) of their parents completed questionnaires. 13 (54%) children were between 16-18yrs of age. 18 (75%) of them were girls. 96% to 100% of the children and parent rated either certainly true or partly true with regards to the attitude and clinical knowledge of the health professionals. Only 83% to 87% of children and parent agreed that their appointments were at a suitable time. When specifically asked about *'what was good about the service'* 16/24 children and 18/24 parent felt that the team listened to them, was very patient, had good knowledge and understanding of the condition, sympathetic, very helpful, concerns taken seriously and believed them. When asked about *'things needed to be improved'* 9/24 children and 9/24 parents felt that they preferred information on alternative therapies and improved communication amongst ward staff and the CFS/ME team if admitted to hospital.

Conclusion:
It is encouraging to see the families' having positive healthcare experience. This survey focussed on the quality of the service delivery. It is vital that in future survey on the effectiveness of the different modalities of treatment they receive would overall improve how we manage children with CFS/ME.

EPIDEMIOLOGY

Profile of the Patient with Chronic Fatigue Syndrome, Experience with a Population-Based Registry

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Objectives:
In Spain, there are no epidemiologic studies analyzing the characteristics of patients diagnosed with chronic fatigue syndrome (CFS) according to the criteria of Fukuda. Thus, the prevalence and incidence of this nosologic condition, which causes considerable disability in personal, social, and work-related activity, is currently unknown. This study determines the sociodemographic, clinical, and therapeutic characteristics of a large series of CFS patients in our setting.

Patients and Method:
All patients who consulted for disabling chronic fatigue and met the diagnostic criteria of Fukuda were included. Patients underwent a diagnostic protocol that included complete laboratory analyses, chest x-ray, abdominal ultrasound, and psychiatric assessment. Sociodemographic data, symptoms, work situation, and treatments prescribed at the time of the diagnosis were recorded. .

Results:
The study included 981 patients with CFS (91 men and 890 women), with a mean age of 47,9 years, 66% were married, 60% carried out specialized work, and 7% were housewives. Among the total, 60% had a secondary school or university education. There was a family background of CFS in 12%, fibromyalgia in 10%, and other immunological diseases in 26.4%. The mean age at the onset of symptoms was 37,5 years and the mean interval from the onset of fatigue to the diagnosis was 116,5 months. The onset was sudden in 20% and gradual in 61%. An evident trigger was documented in 60% (infection, delivery, and a stressful life event). At the time of the diagnosis, 62.5% of patients were not working (sick leave 34% and work disability 37%). The treatment received at diagnosis included medication for the symptoms (analgesic, anxiolytic, and antidepressive agents) in 78,3%, alternative treatments in 3%, and programmed physical exercise and/or cognitive behavioral therapy in 5%.

Conclusions:
When evaluating a patient with incapacitating chronic fatigue, it is essential to identify cases that meet the criteria for CFS. In our setting, this condition predominantly affects middle-aged women who have a secondary or university education and work at specialized jobs. The onset of symptoms often occurs following an identifiable trigger. The condition leads to severe dysfunction in the personal, social, and work-related activities of daily life.

*This study is supported by a research grant (Beca Mutua Madrileña, 2007)

Illness Course in Chronic Fatigue Syndrome – What Can Be Done To Prevent Deterioration and Promote Improvement of Occupational Performance?

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Objectives:
Chronic fatigue syndrome (CFS) often leads to extensive problems with occupational performance. Different disciplines disagree about what treatment strategy is best with regard to improving occupational performance. Few studies are based on the patients' opinion about this issue. This study focuses therefore on CFS patients' understanding of which factors and processes that influence their occupational performance, both before and after they were diagnosed.

Methods:
Semi-structured interviews were used for data collection. The sample consists of 15 women with mean age 42 years (range 31 to 58) that were diagnosed with CFS between 9 months and 17 years ago. All participants met the CDC criteria for CFS. Eight participants had been severely ill and were totally bedridden between 15 months and 7-8 years. All participants still had a mild to severe degree of CFS at the time they were interviewed, but all had improved.

Results:
The participants were diagnosed with CFS from 6 months to 20 years after they became ill. Symptoms changed and fluctuated over time, while they experienced an increasing intolerance for physical and mental activity. Lack of support and understanding, expectations and demands from themselves and others, as well as financial insecurity caused stress and over-exertion that influenced their occupational performance negatively over time. Two participants got bedridden before they got diagnosed. The CFS-diagnosis made it possible to find information about how to cope with the illness. They experienced that pacing activities, energy conservation, rest/relaxation, stress management, lower expectations to themselves, social support, changes in nutrition, financial security, as well as acceptance improved their occupational performance and reduced symptom-fluctuation over time. Some continued with over-exertion after they got diagnosed with CFS and got bedridden. While bedridden they learnt that it was important to be nursed by a few persons, according to routines they had agreed upon and with respect for their symptoms and needs. They needed above all peace of mind, and a feeling that they and their family were taken care of, so that they could use all their energy on getting better. When they started to feel better, they felt that it was important to mobilize in their own pace and not to be pushed by anyone. They improved very much in the same way as those who weren't bedridden, but had to start at a very low activity level. Their intolerance for physical and mental activity improved over time. Some improved quicker after Lightning Process, while others didn't have any effect or just a temporary effect.

Conclusion:
Diagnosing CFS at an early stage may prevent deterioration over time. In addition, patients need information and help in order to cope with CFS in an adequate way. Those who are able to avoid over-exertion stabilise, and improve their occupational performance over time. At the ME/CFS-centre, a multidisciplinary team applies the results of this study when they give advice to CFS-patients about how to deal with the illness at all stages of the illness course.

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Risk Factors for CFS in Women: A Case-Control Study of Gynecologic History

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Objective:
Chronic fatigue syndrome (CFS) is more common in females and is predominantly diagnosed in middle-age. We have previously found, in a Mid-Western population, that CFS in women was associated with endometriosis and hysterectomy and a tendency for earlier menopause. In this study, we used a different female population to examine sex-specific risk factors for CFS in women.

Methods:
A population-based survey in several counties in Georgia, USA, followed up by a nested case-control study. The reproductive histories of 84 women identified as having CFS either at a baseline (2007) and/or follow-up clinical study (2008) were compared to those of 73 women who were well and non-fatigued (controls) both at baseline and follow up. We used Chi square test for comparison of proportions and calculated odds ratios (OR) with 95% confidence intervals (95% CI) to measure the magnitude of associations between CFS and reproductive history variables.

Results:
CFS cases and controls were similar in demographic characteristics and had similar mean age at menarche (12 years). However, women from the CFS group reported significantly more gynecologic problems and surgeries than controls. These included: excessive menstrual bleeding [73.8% vs. 26.2%, OR 3.82 (1.95-7.48), $p<0.001$], bleeding between periods [48.8% vs 23.3%, OR 3.14, $p=0.001$], endometriosis [30.6% vs. 12.3%, OR= 3.01 (95% CI, 1.30-6.98), $p<0.05$], being menopausal [62% vs 37% of controls, OR=2.77, 95% CI, 1.38-5.59, $p=0.002$] and earlier age at menopause [mean±SEM, 37.6±1.3 vs 48.6±0.9 years, $p=0.001$. Compared to controls, women with CFS were significantly more likely to report: any gynecologic surgery [OR=4.12 (95% CI, 2.11-8.04), $p<0.05$], especially hysterectomy [OR=5.10 (2.47-10.52), $p<0.05$], removal of both tubes [OR =2.67 (95% CI,1.14-6.34), $p<0.01$], removal of ovaries [OR=2.07 (0.97-4.41), $p=0.06$]. Gynecologic surgeries in the CFS group occurred at a younger mean age than in controls: mean (±sd) 35. 9 (6.8) vs 41.5 (6.3) years for hysterectomy, 38.7 (sd 8.4) vs 45.1 (3.5) years for removal of both ovaries. Onset of fatigue occurred after surgery in 55% of cases (of those with data available) suggesting that not only removal of the uterus and/or ovaries but also preexisting gynecologic conditions and hormonal abnormalities that lead to these surgeries may predispose to CFS.

Conclusions:
The high prevalence of excessive menstrual bleeding and bleeding between periods among women with CFS as well as the association between CFS and early menopause suggest that hormonal abnormalities with involvement of the hypothalamo-pituitary-gonadal axis may be contributing to the pathogenesis of CFS in women. The possible mechanism of these associations and their implications for diagnosing and treatment of CFS in women remain to be clarified.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agency.

Medication Responses in Chronic Fatigue Syndrome (CFS) And Non-CFS Subjects

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Objective:
There is a clinical perception that Chronic Fatigue Syndrome (CFS) subjects have greater drug sensitivity and "allergy" than the rest of the population. This perception was tested by assessing the symptoms associated with medication use in a group stratified by CFS status and gender.

Method:
194 subjects answered a binary (yes-no) questionnaire (Simon GE, Daniell W, Stockbridge H, Claypoole K, Rosenstock L. *Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity.* Ann Intern Med 1993;119:97–100) to determine if "medications" (not further subdivided by drug class) caused any of 25 symptoms from the neurological (6 symptoms); musculoskeletal (5); airways (7); gastrointestinal (5); and skin (2) systems.

Gastrointestinal- nausea, vomiting, diarrhea, abdominal pain, and heartburn;
Neurologic- headache, dizziness, confusion, memory loss, nervousness, and visual change;
Musculoskeletal- joint pain, joint swelling, muscle pain, weakness, and fatigue;
Pulmonary- cough, runny nose, shortness of breath, sneezing, wheezing, sinusitis & chest pain;
Dermatologic- skin rash and itching

Subjects used our CFS Severity score to estimate the severity of fatigue and the 8 minor criteria for the previous 6 months. The anchored ordinal scale scored 0 for no symptoms, 1 for trivial, 2 mild, 3 moderate and 4 severe. Fisher's Exact Test and T-tests were used to assess significant effects of gender and CFS status.
Result: The subgroup of ALL CFS females had more frequent nausea (32% vs. 13%; p=0.013) and visual changes (19% vs. 4%; p=0.018) than ALL non-CFS females. ALL CFS males had nausea (26%; p=0.003) and dizziness (23%; p=0.006) compared to zero in ALL non-CFS males. However, these differences were misleading because many individuals had no symptoms, and so would not have adverse complaints or contact their physicians. Therefore, the 47% of CFS and 72% of non-CFS subjects with zero symptoms were removed.

The remaining 65 CFS subjects had 5.6 symptoms (4.2 to 7.0, 95% CI). The 20 non-CFS subjects had 3.5 symptoms (1.8 to 5.2; not significant by t-test). Females in these subsets had no significant differences in symptoms frequencies. However, CFS males (n = 22) had more nausea (54.5% vs. 0%; p=0.067) and dizziness (50% vs. 0%; p=0.091) for non-CFS males (n = 4).

Conclusion:
The apparent higher prevalence of medication-related symptoms in CFS than non-CFS was biased by the large number of subjects with zero symptoms. When subjects with no complaints were excluded, there was no difference between CFS and non-CFS females, but a trend for CFS males to have had more gastrointestinal and neurologic symptoms than the non-CFS males. Overall, the equivalence of symptoms in CFS and non-CFS suggests that Multiple Chemical Sensitivity (MCS) may be an independent syndrome. These methods will direct our analysis of other irritants in this multiple chemical sensitivity questionnaire.

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The Epidemiology of Self-Reported Chronic Fatigue Syndrome in Canada

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Objective
To determine for the first time the prevalence of Chronic Fatigue Syndrome (CFS) in the household population of Canadians 12 years of age and over, and to explore its relationship with various key determinants of health.

Methods
Data were obtained from the Canadian Community Health Survey, Cycle 3.1 (2005). Weighted prevalence rates (PRs) for CFS in the Canadian population and specific sub-groups based on various key determinants of health were calculated. The 95% confidence intervals (CIs) around PRs were calculated using exact standard errors generated through bootstrap re-sampling techniques.

Results
In 2005, 331525 Canadians reported having CFS (PR 1.22%, 95%CI: 1.13-1.31), with a female-to-male PR ratio of roughly two to one. The prevalence of CFS among women peaked in the 45-64 age group and fell thereafter, whereas the increase among men was monotonic across all ages. Women in the 45-64 age group accounted for more than a third of all reported cases of CFS. Sub-group analyses based on various key determinants of health showed that people who reported lower income, altered employment status or living in food-insecure households were more likely to report having CFS. A greater PR of CFS was found among people who reported being inactive, dealing with activity limitations, needing help with daily tasks, having difficulty with social situations as well as among those facing discrimination or unfair treatment due to their health condition. Finally, heavy users of health care services as well as those with unmet health care or home care needs showed increased PRs of self-reported CFS.

Conclusions
To our knowledge, this is the first study examining the prevalence of CFS in the household Canadian population and among various sub-groups based on key determinants of health. The PR of self-reported CFS was several-fold higher than the national PR among sub-groups with poorer measures on a variety of health determinants, including determinants of unmet health needs and access to care. Further investigations are required to decipher the true nature of these associations, in order to develop effective preventive and/or disease management measures.

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GENOMICS AND GENETICS

Distinct Clustering of Cerebrospinal Fluid Peptides and Other Ion Peaks in Clusters of CFS and Healthy Subjects

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Objective:
Determine if proteomic differences were present between subsets of CFS.

Method:
Informed consent was obtained from CFS (n=59) and HC (n=18) subjects to have lumbar punctures. Subjects used our CFS Severity Score to estimate the severity of fatigue and the 8 minor (1994 Fukuda) criteria for the previous 6 months. The anchored ordinal scale of scored 0 for no symptoms, 1 for trivial, 2 mild, 3 moderate and 4 severe. Cerebrospinal fluid proteins were digested into peptides with trypsin before Orbitrap mass spectrometry. Ion peaks from mass spectrometry and CFS subjects' Severity Scores were grouped using "two-dimensional" unsupervised hierarchical clustering (MatLab).

Results:
The heatmap defined four clades of CFS subjects (***C1*** to ***C4***, columns) and five clades of ion peaks (***P1*** to ***P5***, rows) (**Figure 1**). Clade ***P1*** ion peaks were equivalent for all CFS clades and ***H1*** (**Table 1**). The exception was a subset of C4 (upper right). ***P2*** ion peaks were ranked ***C3***≈***C4***>***H1***>***C1***≈***C2***. ***P3*** ions ranked CFS in the opposite way: ***C1***≈***C2***>***H1***>***C3***≈***C4***. ***C4*** was significantly different from ***H1*** for peaks in ***P4***. Ions in ***P5*** were ranked ***C3***≈***C2***>***H1***>***C2***. Each ion clade had unique results

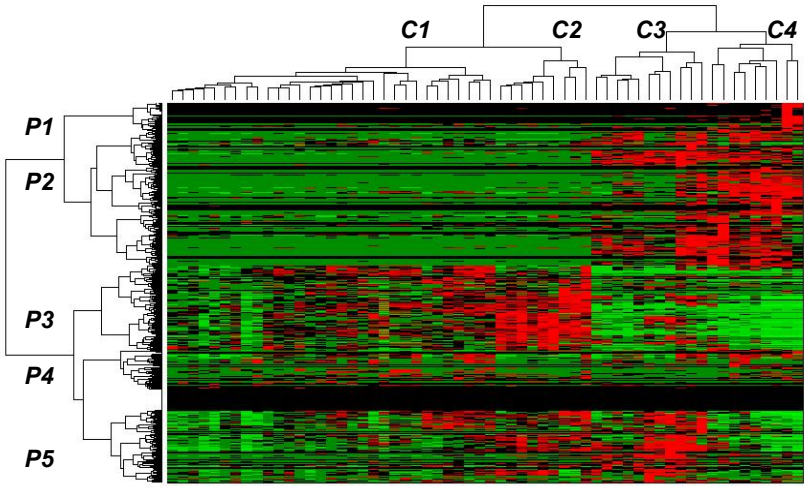

Figure 1. Four CFS clades (***C1*** to ***C4***) and five clades of ion peaks (***P1*** to ***P5***) were delineated by hierarchical clustering. Red indicates close Euclidian distances (close relationships).

Table 1. Significant differences in average ion peak signal intensities were found between CFS clades ***C1*** to ***C4*** compared to ***H1*** using the five ***P1*** to ***P5*** clades of ion peaks.

	C1	*C2*	*C3*	*C4*	*H1*	2-tailed unpaired Student's t-tests vs. *H1*
P1	68,932	60,370	42,627	125,235	82,270	
P2	39,708***	44,831***	133,834 **	152,323***	94,381	
P3	309,733***	337,589***	121,288***	117,454***	241,638	
P4	413,144	257,637	300,121	502,500 *	350,967	
P5	351,551	440,216 *	502,533***	223,307***	376,086	

* $p<0.001$
** $p<0.00001$
*** $p<10^{-10}$

Conclusions:
These distinctive cerebrospinal fluid proteomic patterns for CFS subgroups suggest that distinctive pathophysiological mechanisms that lead to unique protein biosignatures may be associated with clinically defined subsets of CFS subjects.
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GVDR-Fok1 and GVDR-Bsm1 Polymorphisms in ME/CFS Patients

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Objectives:
Several researchers have demonstrated abnormalities in Vitamin D metabolism in ME/CFS patients.
The individual degree of responsiveness of Vit. D binding protein – macrophage activating factor (GcMAF) is according to Ruggiero et al. dependent on Vit. D receptor (VDR) gene polymorphism, which can be identified by Bsm1 and Fok1, two SNPs (single nucleotide polymorphisms). VDR is also involved in skeletal metabolism, modulation of immune response and regulation of cell proliferation and differentiation.
Fok1 is a T-C polymorphism; the T allele leads to a protein which is less effective in transduction of the Vit. D signal, the C allele with a higher response.
Bsm1 is a C-T polymorphism. The C allele is associated with Th1 suppression and breast cancer, the T allele with SLE and RA.
Given the published scientific studies on the immune system in ME/CFS, we hypothesized that both for Fok1 and Bsm1, the incidence of low responders to GcMAF is higher than in the general population, thus predisposing to a lower natural defense to viruses, intracellular bacteria, mycoses and parasites (low Th1/Th2 ratio).

Methods:
185 ME/CFS patients were included in this study.
GVDR-Fok1 & Bsm1 were determined.
Based on Ruggiero's work we know that related to GcMAF:
Fok1: C/C genotype: high responder (FF genotype)
T/C genotype: moderate responder (Ff genotype)
T/T genotype: low responder (ff genotype)

Bsm1: C/C genotype: high responder (bb genotype)
T/C genotype: moderate responder (Bb genotype)
T/T genotype: low responder (BB genotype)

Results:

GVDR (VDR polymorphism) Analysis in 185 ME/CFS patients					
FOK1			BSM1		
	% patients	% control		% patients	% control
FF (high responder)	24	37	bb (high responder)	28	35
Ff (moderate responder)	46	43	Bb (moderate responder)	43	43
ff (low responder)	30	20	BB (low responder)	29	22

A one sided t-test was used to test the hypothesis that the mean % of the Bsm1 BB/Bb/bb and Fok1 FF/Ff/ff groups is statistically different from the average in the normal population according to reference percentages.
For Fok1/Bsm1 ff/BB fenotypes (low responder) were significantly higher than in controls and FF/bb (high responder) were significantly higher in controls ($p < 0.001$).

Discussion:
When compared to the general population, more ME/CFS patients seem to be genetically low GcMAF responders, possibly explaining higher susceptibility for persistent infection.
This finding can be added to the list of genetic predisposition factors which may predispose to the development of ME/CFS.

Purinergic Signaling in Chronic Fatigue Syndrome/ME

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Objective:
Chronic Fatigue Syndrome (CFS) is a multi-factorial disease that involves abnormalties of neuro-endocrine immune function. Presently, a number of neuropeptides have been associated with CFS. This may be attributed to their role in regulating immune function. These neuropeptides are involved in purinergic signaling and their compromise may be associated with receptor differences or other derangements of the adenosine pathway. This study examines the expression pattern of purinergic receptors and the molecules in involved in the signaling pathways.

Method:
Cerebrospinal fluid (CSF) and peripheral blood mononuclear cells (PBMCs) collected from 20 CFS/ME and 5 normal control participants were examined for the expression pattern of the various purinergic receptors and second messenger systems using ELISA and gene expression protocols. Statistical analysis used in this study is ANOVA with p-value set at 0.05.
Result: Preliminary data demonstrated differential distribution of purinergic receptors in CFS participants compared to the healthy controls. Similarly, ATP, cAMP and adenosine were also differentially expressed in the CFS/ME participants compared to the controls.

Conclusion:
These results suggest potential involvement of the CNS in the mechanism of CFS/ME. Further studies are required to assess the potential significance of these findings in CFS/ME.

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Distinct Cerebrospinal Fluid Proteomic Patterns in Clusters of CFS and Healthy Subjects

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Objective:
The protein constituents of cerebrospinal fluid are its proteome. If central nervous system dysfunction contributes to CFS pathophysiology, then proteomes from CFS subjects should differ from healthy controls (HC). If CFS is a homogenous illness, then the patterns of proteins should be similar for all CFS subjects. However, if CFS is a heterogenous disorder, then different patterns of proteins may be found for subsets of CFS subjects.

Method:
Informed consent was obtained from CFS (n=59) and HC (n=18) subjects to have lumbar punctures. Cerebrospinal fluid was digested with trypsin for mass spectrometry. Of the 4,543 ion peaks detected, 880 were peptide ions that matched to 79 proteins (MASCOT software). Unsequenced ion peaks may be complex metabolites, have posttranslational modifications, or be technical artifacts.

Subjects used our CFS Severity Score to estimate the severity of fatigue and the 8 minor (1994 Fukuda) criteria for the previous 6 months. The anchored ordinal scale of scored 0 for no symptoms, 1 for trivial, 2 mild, 3 moderate and 4 severe. Unsupervised hierarchical clustering of Severity Score created a phylogenetic tree with 4 predominant subsets of CFS subjects.

Results:
CFS clades were clade 1 (***C1***; n=31; 41% female; 47 yr), ***C2*** (n=9; 78% female, 52 yr), ***C3*** (n=11; 91% female; 46 yr), and ***C4*** (n=8; 62% female; 48 yr). The healthy control group (***H1***; n=18) had 44% females and average age of 41 yr.
The average signal intensity for all peptide ions in a protein were compared between ***H1*** and the 4 CFS clades by 2-tailed Student's t-tests ($p<0.005$ for significance in this pilot analysis) after ANOVA ($p<0.05$). Proteins with the highest ion counts were NRAP (2 peptides), PTGDS, CAMKK2, ALB (81 peptides), TTR, CST3, TF and CLU. CFS clade 1 (***C1***) had higher levels of CST3, APOE, HP/HPR, APLP1, KLK6, APP, CP and FGA than ***H1***. ***C2*** had 36 proteins with significantly higher average signal intensities than H1. These

included the brain proteins AGT, B3GNT1, GSN, XIRP2, FBLN1, EFEMP1, SPARCL1, CLSTN1, NRCAM, NCAM1, and FN1. Complement proteins included CLU, C3, C4A,B, CFB, and CFH/CFHR1. Serine protease inhibitors were common (SERPINs F1, A3, and D1). The pattern suggested that ***C2*** had higher levels of brain-derived proteins than ***H1***. TTR, SERPINA1 and the neural growth inhibitor DKK3 were significantly higher in ***C3*** than ***H1***. These may also have had predominantly brain origins. ALB counts were highest in ***H1***, and significantly higher than ***C3***. ***H1*** also had significantly higher immunoglobulin peptides, HPX, APOA1, SERPINC1, and SERPINF2 than ***C4***. Half of the proteins that were higher in ***C1*** or ***C2*** than ***H1*** were also higher in ***H1*** than ***C4***.

Conclusion:
CFS phenotypes were defined by hierarchical clustering of CFS Severity Score results. These clades were associated with significantly different panels of proteins. The 4 CFS clades suggest at least 4 pathophysiologically distinct states. Factors that may enrich the brain protein fraction include brain injury with protein release into cerebrospinal fluid (e.g. ***C1*** and ***C2***), and decreased plasma flux across the blood brain barrier (e.g. ***C3***).

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Naglase Activity is A Good Marker For ME/CFS

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Objectives:
The GcProtein or Vit. D binding protein is naturally transformed in the body by intervention of sialidase of T cells and beta-galactosidase of B cells thus removing 2 sugars from the Gc's protein's trisaccharide group, leaving a single sugar at the threonine location. The protein is now GcMAf and can activate macrophages. Previous research has shown that the enzyme alpha-N-acetylgalactosaminidase, called Nagalase, removes the entire trisaccharide group. Deglycosylated GcProtein cannot activate macrophages.
Because ME/CFS patients often have reduced macrophage / NK cell function we hypothesized that Nagalase activity would be elevated in these patients.

Methods
Serum Nagalase activity was determined in 395 ME/CFS patients who met both the Canadian clinical criteria for ME (2003) and the Fukuda criteria for CFS (1994). The Nagalase assay was performed on serum. The blood was centrifuged within one hour of venous blood drawl and serum was frozen immediately till assayed. The assay method used is described in J. Med. Virol. 81:p.9 (2009) by Yamamoto et al. Healthy control sera exhibit very low enzyme activities.

Statistical Analysis:
A one-sided t test was used to test the hypothesis that the mean value of the ME group is significantly different from the middle of the normal range (representing the normal population).

Results:
Average serum Nagalase activity was 1.72 nmol/min/mg (range 0.28-4.0). This is significantly higher compared to levels in normal controls (0.35-0.68 nmol/min/mg) (Yamamoto, 2009).
Only 12 of 395 patients had a Nagalase activity below 0.69 nmol/min/mg, or 3 % of the study population.

Conclusion:
When tested in a large cohort of ME/CFS patients, serum Nagalase is increased in 97 % of the study population.
Irrespectively of the cause of these findings, serum Nagalase activity is a good marker to distinguish healthy people from ME/CFS patients.
These data provide indirect evidence for low macrophage activity in ME patients.

ADVANCES IN BRAIN FUNCTIONING & NEUROENDOCRINE

Neurocognitive Impairment in Chronic Fatigue Syndrome: Complained Symptom or Real Deficit? - An Objective Method of Evaluation

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Objective:
Several symptoms reported by chronic fatigue syndrome (CFS) patients - including fatigue, headache, impaired concentration, attention and memory - suggest that the central nervous system may be involved in the pathophysiology of the syndrome. Coexisting psychological distress or a psychiatric disorder also may contribute to neurocognitive (NC) deficits. Since CFS shows a significant

overlap with Fibromyalgia syndrome (FM), a comparison of the two groups of patients could be important to understand the relationship between fatigue and NC disorders.
The aim of the present study is to investigate the prevalence of NC deficits in CFS patients compared to FM patients, using a standardized set of validated tests, and to understand how psychiatric disorders and intake of psychoactive drugs may interfere.

Methods:
49 patients with a diagnosis of CFS (based on Fukuda criteria, 1994) and 26 patients with a diagnosis of FM (ACR criteria, 1990) were consecutively recruited. Patients with axis I current psychiatric diagnosis were excluded. Each CFS or FM patient was asked to fill a set of questionnaires on paper and perform a battery of NC computerized tests after blood analysis (9:00 am). CNS Vital Signs© (CNSVS)[1] is a NC test battery developed as a routine clinical screening instrument. It is composed of 7 tests for the evaluation of Composite Memory, Verbal and Visual Memory, Processing Speed (PrS), Executive Function (EF), Psychomotor Speed (PsS), Reaction Time, Complex Attention (CA) and Cognitive Flexibility (CF). It returns a score for each item and a composite NC global score named Neurocognition Index (NCI), normalized for patient's age, school attendance and computer usage frequency.

Results:
Patients with CFS (♀ 26/49) had a mean age (SD) of 37.8 (11.5) years, while patients with FM (♀ 24/26) had a mean age (SD) of 43.0 (10.3) years (p=0.017). On a total of 75 patients, only 20 (26,6%) did not complain about NC problems. NCI was higher in CFS subjects (p= 0.02) and 16 CFS patients (32.7%) showed a real NC impairment, vs 12 (46.2%) with FM, considering a real deficit with a low or very low NCI. The items that differed the most were the PsS, the EF and the CG. PsS of all the patients correlated with disease duration (p=0.0004). Of the 55 patients with CFS and FM who complained about NC disorders, less than half showed low or very low NCI. Thirty-five patients out of 75 had not a psychiatric lifetime comorbidity, 20 patients (26.7%) had a mood disorder and 20 (26.7%) an anxiety disorder. Patients with such a comorbidity had a lower NCI (p=0.0044), in particular lower CA, PrS, CG, PsS and EF, independently on the diagnosis. Moreover, 23 out of 75 patients were taking antidepressant drugs (AD) and 18 benzodiazepines (BDZ). Between patients treated with BDZ and those treated with AD there were not significant differences.

Conclusion:
The 32.7% of CFS patients showed a real NC deficit, although the 68.6% complained about it. FM showed more severe NC impairments respect to CFS patients, independently on drug assumption and age. A deficit of neurocognitive functions seemed to be predominant in patients with psychiatric lifetime comorbidity, independently on the assumption of antidepressant or anxiolytic drugs and the diagnosis. Thus, CNSVS has proven to be a useful and easy tool for the assessment of NC impairments in clinical trials as well as in routine practice.

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The TeleHealth Study: Memory Problems in Patients with Chronic Fatigue and Their Psychosocial Impact

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Objectives:
Present preliminary findings from the TeleHealth Study, a 4-year randomized trial that evaluated a technology-based intervention for individuals diagnosed with Chronic Fatigue Syndrome (CFS). This presentation will focus on the prevalence of memory problems in individuals with CFS and their impact on psychosocial outcomes such as social interaction/engagement and depression.

Methods:
Baseline interview data was evaluated from a sample of 116 CFS participants including 19 males and 97 females who ranged in age from 23 years to 73 years. The sample was primarily Caucasian (78.4%) and most participants had beyond a high school education (89.6%). Two independent variables were analyzed to evaluate possible cognitive deficits reported by study sample, in particular memory problems such as forgetfulness and confusion. Frequency of forgetfulness was obtained from the CDC Symptom Inventory and reported feelings of confusion-bewilderment from the Profile of Mood States (POMS) confusion- bewilderment subscale. The psychosocial impact of these cognitive problems was further analyzed by examining the relationship between these cognitive problems and the participant's levels of social interaction/engagement and symptoms of depression. The Sickness Impact Profile (SIP) subscales measuring disruption in social interaction and engagement in recreation/past times, and the Center for Epidemiologic Studies Depression (CES-D) score and the POMS depression-dejection subscale were used as dependent variables in the analyses.

Results:
The analyses revealed that nearly 88% of the study sample (N = 102) reported having experienced forgetfulness/memory problems that caused them to substantially cut back on activities since the onset of CFS. Of those who reported experiencing forgetfulness/memory problems, 65% indicated experiencing these symptoms everyday at moderate (45.1%) to severe (33.3%) levels. A one-way ANOVA demonstrated that those participants who experienced forgetfulness/memory problems reported greater social isolation scores, $F(1,114)=11.215$, $p=0.001$, and less engagement in leisure activities, $F(1,114)=5.912$, $p=0.017$. Higher scores on the

POMS confusion-bewilderment subscale were also correlated with greater social isolation, r(114)=.448, p<.001 and less leisure activities, r(114)=2.16, p=.020. Greater amounts of confusion-bewilderment was also related to high levels of depression symptomatology as measured by the CES-D, r(114)=.653,p<.001 and the POMS depression-dejection scale, r(114)=.674,p<.001.

Conclusion:
A significant number of CFS patients report having memory problems that interfere with their daily activity and affect their mood and ability to engage in social activities. Those patients with memory problems are particularly at risk of being socially isolated and depressed. Overall these results suggest that future interventions for these patients should also focus on strategies to help remediate memory problems.

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Gulf War Illness: Effects of Exercise on Working Memory

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Objectives:
Over 25% of the active duty military personnel from the First Persian Gulf War developed chronic multisymptom complexes that included Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, and Post Traumatic Stress Disorder. These overlapping disorders form Gulf War Illness (GWI). This heterogeneous disorder presents challenges to delineating underlying causes as well as targeted treatment. We used fMRI to examine the effects of an exercise stressor on working memory to help phenotype subtypes of GWI.

Methods:
Veterans were eligible if they were active military duty for at least 30 days from 1990-1991. 18 veterans (average age 50; 12 male) were included. Subjects had identical fMRI protocols before and after VO2max bicycle ergometer stress tests that were done on consecutive days.

Participants were trained outside of the scanner until proficient in the N-Back paradigm, which requires continual encoding and retrieval of information. Stimuli consisted of single letters (A, B, C, or D) presented randomly. The task was presented using a block design alternating between 0-Back and 2-Back. For 0-Back, participants pressed the correct button corresponding to the letter presented. 2-Back required pressing the button corresponding to the letter presented 2 letters earlier. Accuracy scores were used to separate participants into two groups: those who performed better after exercise and those who performed worse.

Functional MRI data was acquired on a 3.0 T Siemens TIM Trio MRI scanner. Data were analyzed using SPM5 using a mixed-effects statistical analysis examining the brain activity for 2-Back>0-Back during the pre- and post-stressor sessions for each group.

Results:
Ten participants had increased accuracy: 0-Back by +3.12% (ceiling effect) and 2-Back by +19.8%. 8 subjects had decreased performance: 0-Back by -9.74% and 2-Back by -11.1%.

The increased accuracy group showed greater activation after exercise in the caudate (p<0.001) and precuneus (p<0.001). These are task related areas, indicating that this group of subjects recruited more cognitive resources to perform better after exercise.

In contrast, those with decreased accuracy after exercise had less activation (p<0.001) in the dorso-lateral prefrontal cortex (DLPFC). While this area is also reliably activated by the N-Back, decreased DLPFC activation reflects cognitive inefficiency and failure to recruit additional resources.

Conclusion:
The group that demonstrated improved accuracy also showed increased activation in task-related areas, indicating that this group received cognitive benefits from exercise. However, the group of GW patients that suffered exercise related working memory deficits showed decreased DLPFC activation after exercise. This significant change points to their inability to recruit cognitive recourses during exercise-induced fatigue. These two distinct responses to exercise are one indication that the heterogeneous GWI can be subdivided for more targeted treatment.

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PATHOPHYSIOLOGY

Heart Rate Variability Evaluated with the LF/HF Ratioi of Sympatetic-Parasympathetic Activity in the Assessment of Neurovegetative Dysfunction in Patients with Chronic Fatigue Syndrome and No History of Syncope

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Objective:
In chronic fatigue syndrome (CFS) neurovegetative symptoms have acquired relevance through the Canadian diagnostic criteria. As is the case of other highly disabling symptoms of this condition, resources are needed to quantify these neurovegetative manifestations. We propose assessment of heart rate variability by means of the LF/HF ratio determined on orthostatic positioning with tilt table testing in CSF patients with no prior history of syncope.

Patients and Method:
The study included patients with no history of syncope, diagnosed with CFS according to the Fukuda criteria. Neurovegetative, muscular, neurocognitive, and immunologic symptoms were recorded. Patients were evaluated with the fatigue impact scale (FIS), SF-36 quality of life questionnaire, hospital anxiety and depression scale (HADS), and stress testing (maximum oxygen consumption, maximum cardiac output, maximum heart rate, and energy expenditure). Biological markers were determined (RNase L ratio, RNase L activity, elastase activity, and serum nitric oxide concentration). The LF, HF and LF/HF ratio were evaluated on tilt table testing, with 3 determinations 5 minutes apart in supine position and 8 in orthostatic position. The *t*-test for paired samples was used to analyze trends. Associations between variables were examined with the chi-square test, *t* test, or Mann-Whitney test.

Results:
Thirty-seven CFS patients were studied (4 men, 33 women), with a mean age of 48 years; 65% had a gradual fatigue onset, and the interval from onset to diagnosis was 136 months. Neurocognitive, muscular, and immunologic symptoms were present in 95%, 87%, and 78% of patients, and neurovegetative symptoms in 90%. The total FIS score was 131.8, physical subscale 35.6, psychosocial 62.3, and cognitive 40. The SF-36 physical health score was 25.7 and mental health 36.1. The anxiety-depression component was 11.3. In addition, maximum oxygen consumption 57.1%, maximum cardiac output 67,1, maximum heart rate, 115.6 bpm and energy expenditure 4,6. RNase L ratio was 0.54, RNase L activity 16,9 elastase activity 198,3, and nitric oxide 7.35. Differences in the heart rate variability parameters (LF, HF and LF/HF ratio) were found between supine position and at 5 minutes of orthostatism, with an increase in the LF or sympathetic component. During the next 30 minutes in orthostasis, no changes were observed in the LF/HF ratio, with persistence of the excess sympathetic response. The mean LF/HF ratio was 4.88 and a significant association was found with the presence of Raynaud phenomenon, altered libido, SF-36 role-emotional and total mental health, and the depressive component on the HADS, as well as considerable (but non-significant) associations with the FIS psychosocial subscale (p=0.08)and RNase L (p=0.09) ratio.

Discussion:
In patients with CFS and neurovegetative symptoms without prior syncope, a maintained, predominantly sympathetic neurovegetative response, as assessed with the LF/HF ratio of heart rate variability, was seen on tilt table testing.
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Impact of Neurovegetative Symptoms on Patients Who Are Diagnosed With CFS And Have No History of Syncope

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Objective:
Neurovegetative symptoms, such as dizziness, syncope, abnormal intestinal and bladder rhythms, sweating, and accommodation , were not initially contemplated in the diagnostic criteria of Fukuda for CFS. They acquired more importance later, when the Canadian criteria were established. In this study, the impact of neurovegetative symptoms is investigated in a group of patients with no prior history of syncope and a diagnosis of CFS.

Patients and Method:
The study included patients with no history of syncope, diagnosed with CFS according to the Fukuda criteria. Sociodemographic and work-related variables, symptoms, and comorbid phenomena were recorded. The impact of fatigue was assessed with the fatigue impact scale (FIS), SF-36 quality of life questionnaire, hospital anxiety and depression scale (HADS), and the maximum oxygen consumption, maximum cardiac output, maximum heart rate, and energy expenditure on stress testing. Biological markers were determined in peripheral blood monocytes (RNase L ratio, RNase L activity and elastase activity), and serum nitric oxide concentration was measured. Symptoms from the neurovegetative, neurocognitive, muscular, and immunological groups were categorized using the Cronbach alpha value. Associations between neurovegetative symptoms and the remaining variables were studied.

Results:
Thirty-seven CFS patients (4 men, 33 women), with a mean age of 48 years were studied. Among the total, 60% had a middle school educational level and specialized jobs, 65% reported a gradual symptoms onset, and the interval from symptoms onset to the diagnosis was 136 months. Neurocognitive, muscular, and immunologic symptoms were present in 95%, 87%, and 78% of patients, respectively. Neurovegetative symptoms were documented in 90%. Myofascial syndrome was found in 84%, dry syndrome 86%, and tendinopathy 62%. The total FIS score was 131.8, physical subscale 35.6, psychosocial 62.3, and cognitive 40. The SF-36 physical health score was 25.7 and mental health 36.1. The anxiety-depression component was 11.3. In addition, maximum oxygen consumption 57.1%, maximum cardiac output 67.1, maximum heart rate, 115.6 bpm and energy expenditure 4.6. RNase L ratio 0.54, RNase L activity 16.9, elastase activity 198.3, and nitric oxide 7.35. There was a significant association between neurovegetative dysfunction and the presence of painful lymph nodes (p=0.012), food intolerance (p=0.013), and monocyte elastase levels (p=0.02).

Discussion:
In CFS patients with no prior history of syncope, a considerable deterioration in quality of life and physical functional capacity was found, as well as high scores on the fatigue and anxiety-depression scales. Neurovegetative symptoms were common and showed a significant association with immunological symptoms and intracellular parameters of inflammatory activity.

*This study was supported by a grant from the Spanish Ministry of Health and Consumer Affairs (FIS PI050200).

TILT Testing to Assess Neurovegetative Dysfunction in Patients with Chronic Fataigue Syndrome (CFS) and No History of Syncope

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Objective:
Neurovegetative symptoms are very debilitating in CFS patients and there are few available resources to measure, quantify, or treat them. In this study we investigate the neurovegetative response to orthostatic positioning with the use of a tilt table in CFS patients with no prior history of syncope.
Patients and Method:
The study included patients diagnosed with CFS according to the Fukuda criteria, with no history of syncope. Data were compiled on patients' neurovegetative symptoms, scores on the fatigue impact scale (FIS), hospital anxiety and depression scale (HADS), and SF-36 quality of life questionnaire, physical capacity results (maximum oxygen consumption, maximum cardiac output, maximum heart rate, and energy expenditure) during stress testing, biological markers including monocyte RNase L ratio, RNase L activity, and elastase activity, and serum nitric oxide concentration. The following variables were evaluated on tilt table testing: heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, systolic volume, and peripheral vascular resistance (PVR), with 3 determinations 5 minutes apart in the supine position and 8 in orthostatic position.

Results:
Thirty-seven CFS patients were studied (4 men, 33 women), with a mean age of 48 years at diagnosis, 65% with a gradual onset, and an interval from onset to the diagnosis of 136 months. Neurovegetative symptoms were documented in 90%. The total FIS score was 131.8, physical subscale 35.6, psychosocial 62.3, and cognitive 40. The SF-36 physical health score was 25.7 and mental health 36.1. The anxiety-depression component was 11.3. In addition, maximum oxygen consumption was 57.1%, maximum cardiac output 67,1, maximum heart rate, 115.6 bpm and energy expenditure 4.6. RNase L ratio was 0.54, RNase L activity 16,9, elastase activity 198,3 and nitric oxide 7,35. Tilt table testing was positive in one patient with a mixed cardiovascular response. There were no asymptomatic cardiovascular responses, such as orthostatic intolerance, postural tachycardia or hypertensive tachycardia . Significant differences in the cardiovascular parameters were found between supine position and at 5 minutes of orthostasis, with a pattern characterized by a considerable increase in the PVR, and a smaller increase in systolic blood pressure, with a decrease in the systolic volume and cardiac output. Once the orthostatic position was stabilized, there were no changes in the cardiovascular parameters over the next 30 minutes, with persistence of this predominantly sympathetic response.

Discussion:
In patients with CFS, neurovegetative symptoms, and no prior history of syncope, a predominantly sympathetic noradrenergic response is elicited with tilt table testing.
This study was supported by a grant from the Spanish Ministry of Health and Consumer Affairs (FISPI050200).

Effects of Exercise on Systemic Hyperalgesia in Gulf War Illness patients with Chronic Fatigue Syndrome

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Objectives:
Thumb pressure tenderness (TPT) is an indicator of systemic hyperalgesia. Post exercise malaise is a chief complaint of Chronic Fatigue Syndrome (CFS). We expect two days of bicycle exercise stress test to increase systemic hyperalgesia in Gulf War Illness (GWI) patients with Chronic Fatigue Syndrome.

Method:
We tested changes in systemic hyperalgesia in 14 GWI patients with CFS. Systemic hyperalgesia was measured by applying precisely controlled pressures to the thumb nail bed. Pressures were applied in ascending and descending fashion for 3 complete cycles, then 1 randomized cycle to eliminate patient expectation of pain levels. After each pressure, subjects reported their level of pain on a 0 to 20 point anchored ordinal scale. TPT test started at 5 pounds per square inch (psi) and ascended by 5 psi increments until subjects rated pain levels of at least 12 out of 20. Then, starting from the last highest psi, decreasing pressures by 5 psi increments were applied until a final pressure of 5 psi. Subjects completed two days of 25minute 70% maximum heart rate submaximal bicycle exercise stress test. TPT testing was performed on the first day (d1), before first exercise stress test on the second day (d2), and after second bicycle exercise stress test on the third day (d3). The plots of ascending/descending painpressure curves and random pain pressures were plotted and analyzed using Microsoft Excel.

Results:
A hysteresis pattern was observed in the ascending and descending cycle of the pain as function of pressure plots (PfPP). Patients consistently reported higher pain levels on the descending limb of the cycle compared to the ascending limb at the same pressures. The decreasing pressure limb generally had consistent, high pain ratings, even though the pressures were decreasing. Pain reports subsequently dropped rapidly to near 0 at 5 psi. The area between the ascending and descending limb of the PfPP generally decreased from d1 to d3 ($P<0.01$). This may indicate a learning effect by the subject being able to assess
and report pain levels more reproducibly on d3 compared to d1. PfPP of randomized TPT testing on each day showed lower slope values postexercise compared to d1 preexercise ($P<0.0002$). A lower slope indicates lower pain levels at same pressure. This demonstrates a decrease in systemic hyperalgesia after two days of exercise stress testing.

Conclusion:
Thumb pressure tenderness testing effectively measures systemic hyperalgesia. Subjects perceived their nociceptive input on d3 more accurately than d1. This may indicate a spinal or supraspinal adaptation. *Decrease* in systemic hyperalgesia post exercise may indicate mechanism for benefit of exercise to GWI with CFS.

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Blunted Nasal and Systemic Sympathetic Reflexes in Chronic Fatigue Syndrome

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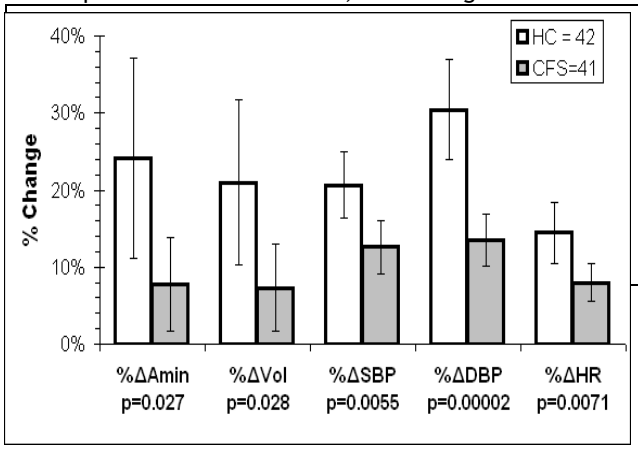
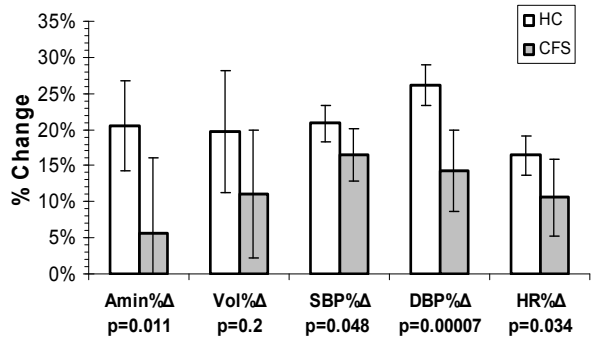
Objective:
Almost 73% of chronic fatigue syndrome (CFS) subjects have a form of nonallergic rhinitis that may be due to autonomic dysfunction. Isometric handgrip was used as a stimulus for sympathetic cardiovascular effects including tachycardia and the vasoconstriction of peripheral and nasal mucosal blood vessels that leads to hypertension.

Methods:
Isometric handgrip tests were performed in 41 CFS and 42 healthy control (HC) subjects. Nasal acoustic rhinometry to measure the volume of the nasal airspace and minimum cross-sectional area at the anterior nasal valve, and vital signs were measured during a sham period of no contraction, and during forearm and hand contraction to 30% of maximum strength.



Results: Although HC were stronger then CFS, there were no differences in duration, pain intensity or tolerance of the handgrip. Incremental changes in vital signs were significant ($p<0.0005$) at exhaustion for both groups. However, only HC had significant increases in nasal Volume and Amin from sham. The % change was significantly greater for HC than CFS for Volume, Amin, SBP, DBP and HR. Some CFS subjects had paradoxical decreases in Volume and Amin, and no changes in vital signs.



The study was repeated in 104 CFS and 60 HC (87 CFS and 55 HC had acoustic rhinometry). Significant differences were found for Amin%Δ, SBP%Δ, DBP%Δ and HR%Δ. Gender differences were present. DBP%Δ was significantly greater for HC females (29%; 20% to 38%) than CFS females (13%;10% to 16%; p=0.00005). HR%Δ was significantly greater for HC males (20%; 11% to 29%) than CFS males (9%; 6% to 12%; p=0.018).

Conclusions:
CFS had significantly lower sympathetic effects on heart rate, blood pressure, and nasal vascular vasoconstriction than HC subjects in response to isometric exercise. Averaged acoustic rhinometry results were variable for CFS suggesting subsets with normal and hyporesponsive effects. One pattern of interest was found in CFS subjects who had immediate increases in all measurements when isometric contractions began, but decayed to smaller or negative %Δ with time. Frequency distributions of these responses may identify CFS subsets with dysfunctional "on-demand" sympathetic discharge. These data support neurological dysfunction of mucosal and systemic sympathetic reflexes in the pathogenesis of CFS and the nonallergic rhinitis of CFS.

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An Hybrid 70% Plus 85% Predicted Heart Rate Bicycle Stress Test Performed on Two Consecutive Days

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Objective:
Determine the merits of submaximal and maximal bicycle stress tests for Gulf War Illness (GWI), CFS and healthy veterans and controls (HC) for tandem, 2 day testing.

Methods:
Subjects exercised on a Schwinn bicycle ergometer. Cardiopulmonary function was measured using mouthpieces and Vmax software. 27 GWI and 8 HC participated in 3 bicycle exercise stress test protocols:

#1. 13 GWI and 2 HC had standardized ramped VO2max tests with exercise until physical limitations caused the test to end (*85%HR*).

#2. 6 GWI and 4 HC cycled at 70% of maximum predicted heart rate for 25 min then accelerated to 85% without cardiopulmonary testing (*70%+85%*).

#3. 11 GWI and 5 HC had VO2max tests that began with 25 min at 70% maximum heart rate that was followed by acceleration to 85% (*70%+85%* plus VO2max).

Symptomatic Responses:
Borg Dyspnea Scores were significantly higher for GWI subjects on DAY 1 (3.9; 2.8 to 4.9 [mean; 95% C.I.]; n=25) and DAY 2 (4.1; 3.1 to 5.0) than HC (1.4; 0.1 to 2.6; n=9; p=0.016 by t-test; and 1.3; -0.1 to 2.6; p=0.0053; n=8; respectively). On DAY 1, whole body pain and fatigue scores at rest and after exercise were in the 3 to 15 range on the 20 point anchored ordinal Gracely Scale for GWI (n=15) compared to 0 to 3 for HC ($0.032 \geq p \geq 0.00005$; n=8). DAY 2 results were marginally higher at 6 to 16 for GWI and 0 to 5 for HC ($0.043 \geq p \geq 0.0000004$). None of the HC subjects complained of pain or fatigue on either day.

Adverse Events:
Protocol #1. Three GWI had to stop because of fatigue and dyspnea with VO2max at 25%, 32% and 50% of predicted. A fourth had dyspnea and oxygen desaturation (88% by pulse oximetry). A fifth GWI subject stopped because their systolic blood pressure dropped by 22% as they neared 70% HR. Protocol #2. Two GWI had to stop after 25 min at 70% of maximum HR because of fatigue or muscle pain. A third GWI subject increased their HR by only 29% before stopping. Protocol #3. One GWI became so exhausted after 70% HR that within 15 minutes he had fallen asleep for 1 hour. One veteran who was otherwise healthy on examination could only exercise to VO2max of 48% of predicted before stopping because of dyspnea on both DAYs. This subject and another otherwise healthy appearing veteran both demonstrated orthostatic tachycardia (ΔHR>30 bpm).

Energy Expenditures:
In the two *70%+85%* protocols, HC expended more METs to reach 85%HR (7.95; 7.08 to 8.82) than GWI (4.94; 4.16 to 5.72; p=0.0015). On DAY 2, this significant difference was found for 70% HR in HC (5.00; 4.26 to 5.74; n=4 vs. 3.17; 2.54 to 3.80; n=6; p=0.0064). At

85% HR the variance of the GWI data was too large for a significant difference to be detected. Expenditures by GWI subjects were different on DAY 2 from DAY 1. Watts needed to reach 85% HR in ramped exercise for GWI were higher on DAY 1 (202; 160 to 245; n=13) than DAY 2 (170; 138 to 202; n=12; p=0.015 by paired t-test). In contrast, the 70%+85% protocol required more calories on DAY 2 (179; 155 to 203; n=12) than DAY 1 (162; 132 to 191; p=0.033) in a different group of GWI subjects. HC had no differences in energy requirements between DAY 1 and DAY 2.

Conclusion**:**
The **70%+85% VO2max test** was the optimal provocation.

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