

CFS/ME Review

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Kroniskt Trötthetssyndrom CFS/ME Illness of Many Names

**Myalgic
Encephalomyelitis
(ME)**

**Low Natural Killer
Cell
Syndrome**

Yuppie Flu

**Chronic Fatigue
Syndrome**

**Chronic Fatigue
Immune
Dysfunction
Syndrome**

- In the US, approximately 10% of the patients consume 70% of all healthcare dollars. Of this amount, a significant proportion is encountered by the diagnosis and management of chronic disease.
- CFS/ME is a significant contributor to the financial burden, as well as functional disability of the society at large.

Annual Economic Loss Due to CFS/ME

\$ 9 billion USD

\$ 1.6 billion

Swedish Kronor



Economic Impact of ME/CFS, Individual and Societal Cost *

Background: CFS presents as debilitating fatigue accompanied by physical and cognitive symptoms.

- Economic impact of an illness is divided into direct and indirect costs.
- High prevalence rate and disabling nature suggested high-cost of ME/CFS to individual and society.

Results:

- Using ME/CFS prevalence of 0.042 indicate total annual direct cost of \$8,675 per ME/CFS patient or a total cost to society of US \$9 billion.
- Direct cost determined by medication usage, self-reported use of physicians, medical testing, and medical office visits.

Economic Impact of ME/CFS, Individual and Societal Cost (cont)

Discussion:

- These economic losses have substantial long-term impact on ME/CFS patients' standard of living and quality of life.
- High unemployment rates increase the cost burden and become even more problematic to individuals and families.
- In addition to direct medical cost imposed on individuals and society, substantial economic loss is related to lost productivity.
- Indirect cost to individual and society represent an addition annual loss of approximately \$20,000/patient. The estimated indirect cost in the US \$17 billion.
- .

Together indirect and direct costs due to ME/CFS estimated to \$17-24 billion/yr.

Myth #1:

ME/CFS is a relatively rare disorder

Facts:

- Prevalence in U.S.
400-600 per 100,000 people
- Number of people affected in U.S.
800,000 people
- Number of people affected in Sweden
32,000 – 40,000 people

Myth #2:

The highest prevalence is among young, affluent, white professionals

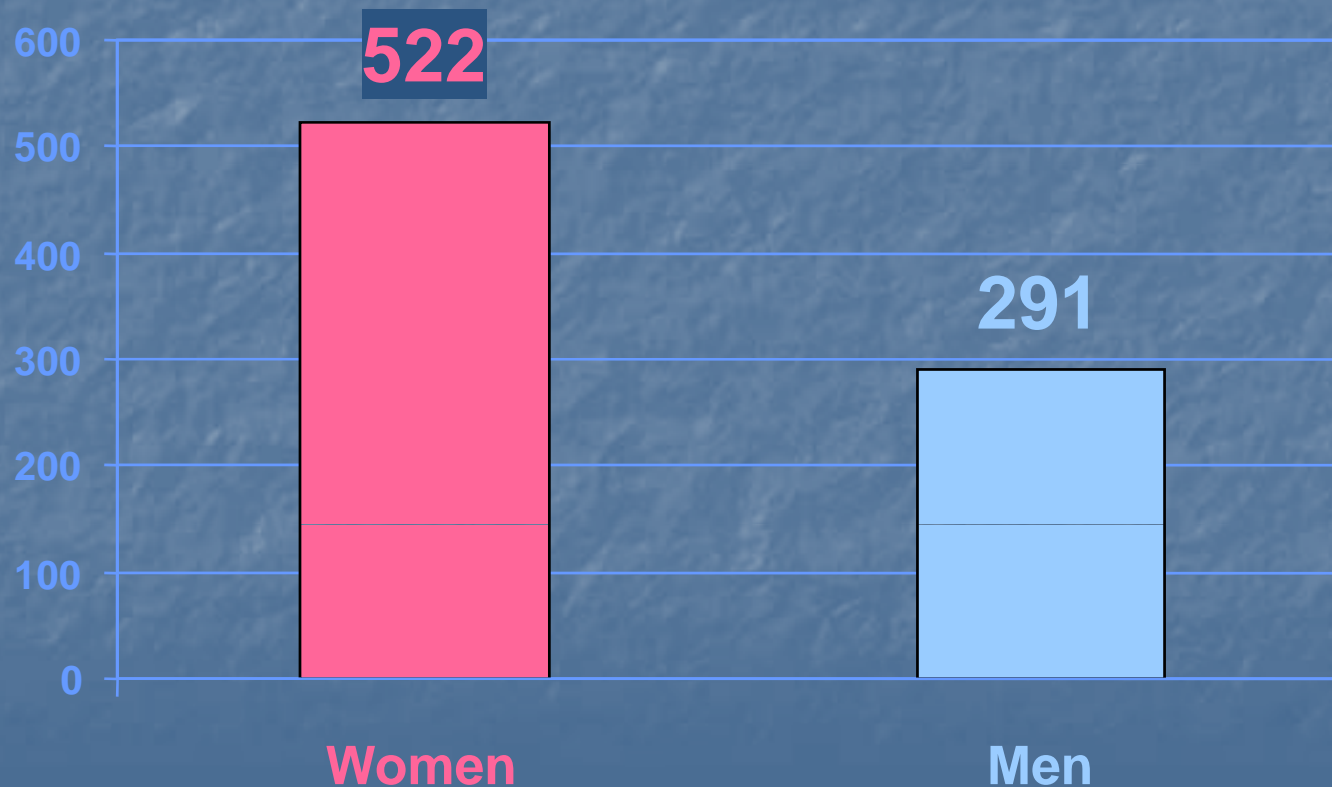
Fact:

Women, men and children from all socio-economic backgrounds are affected by CFS

Fact: Gender

Women have a much higher rate of CFS than men

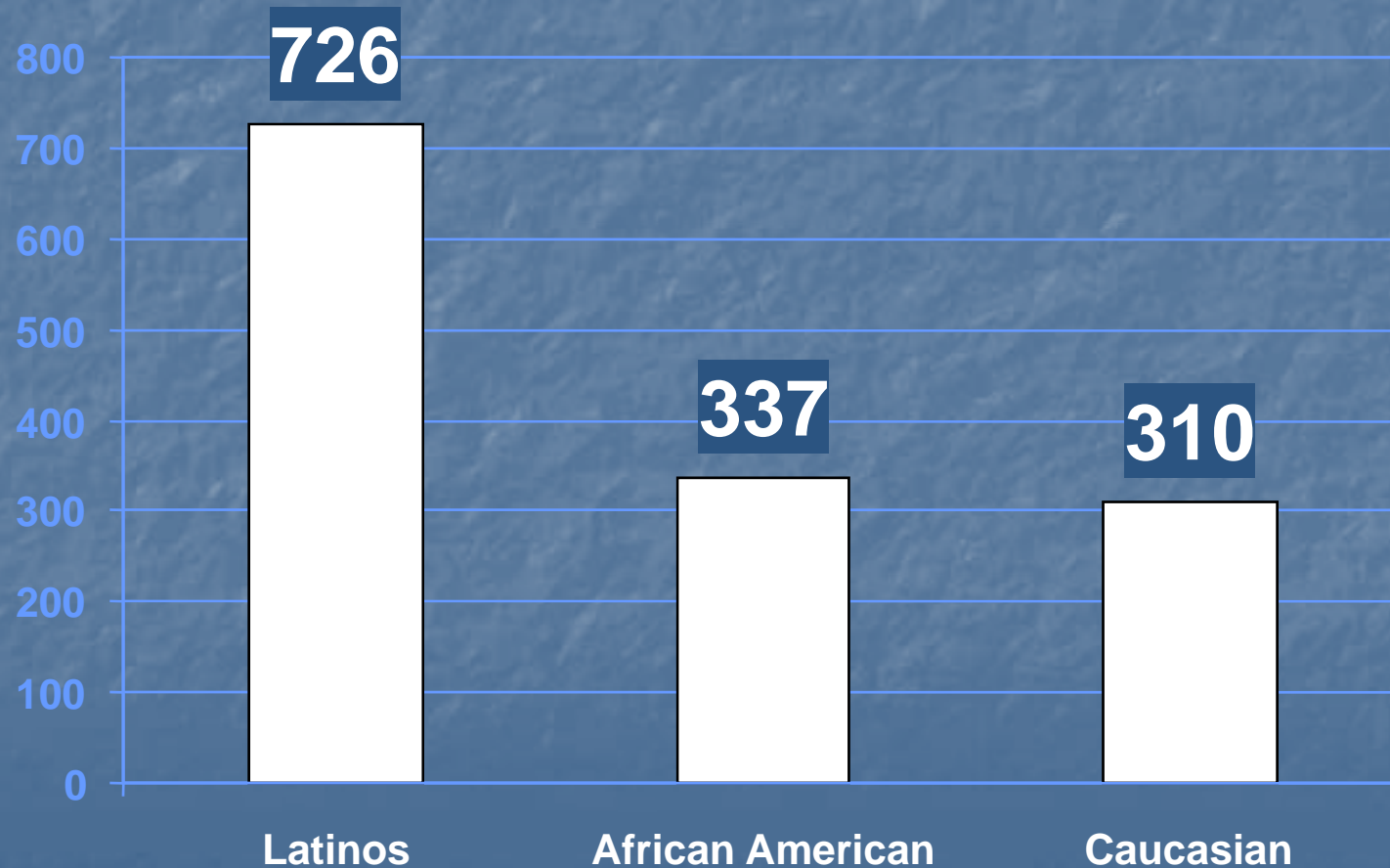
Prevalence by Gender (Per 100,000)



Fact: Race

Latinos have highest prevalence of CFS

Ethnic Prevalence (Per 100,000)



Overlooked Population

Fact:

Children with CFS are under-recognized and under-studied.

“I want to be back in school with my friends. I want to be a normal kid again.”

—Child, age 13

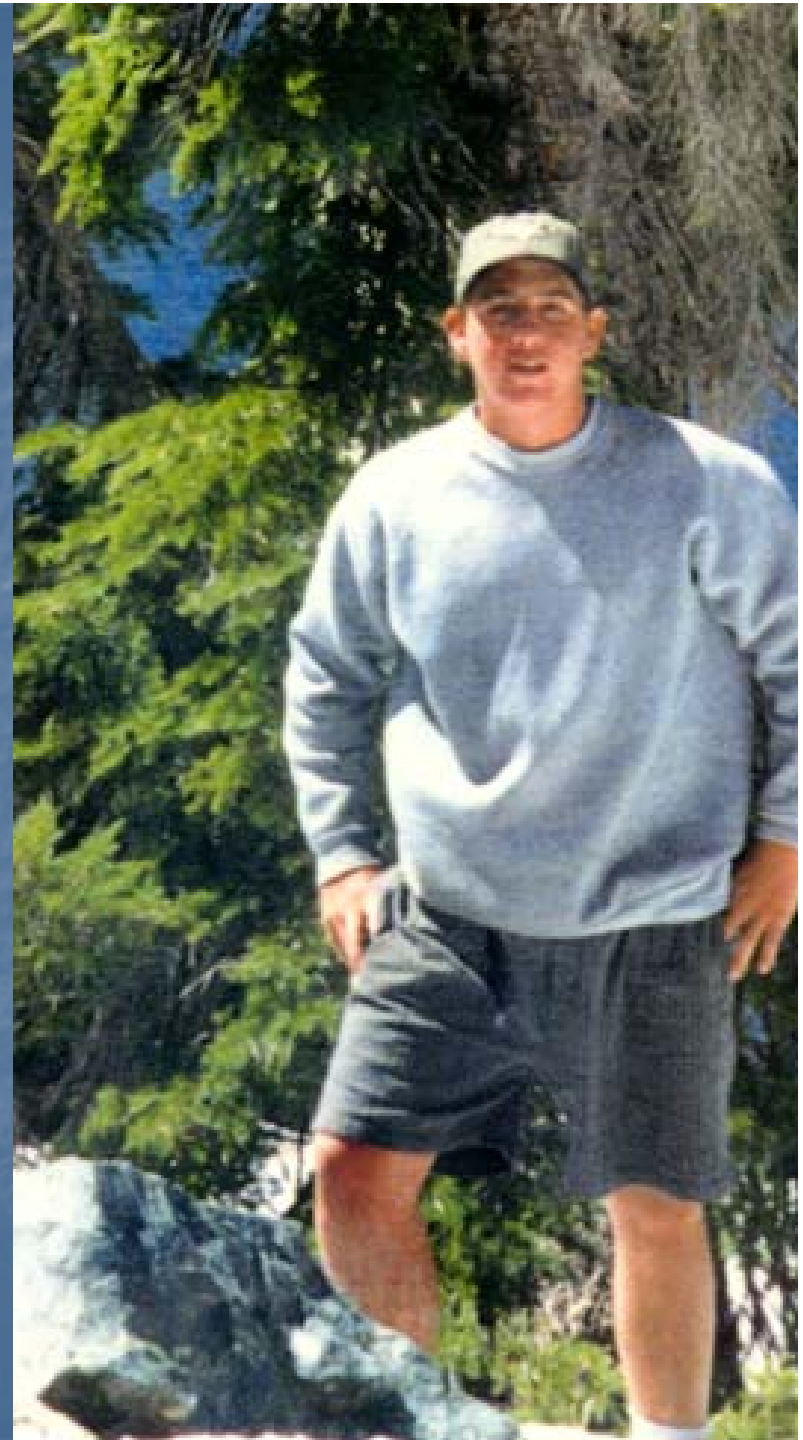
The CFIDS
Association of
America, Inc.
PO Box 220398
Charlotte NC
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CFIDS
a n d
CHILDREN

Pediatric CFS

- Has significant impact on educational achievement
- May result in significant health identity confusion and prolonged disability

David Bell, M.D.
Lyndonville Pediatric Study



Classifications:

-ICD

-WHO

ICD9-CM

- US currently uses the International Classification of Diseases, Ninth Revision
 - 780.71 Chronic Fatigue Syndrome

Difficulties:

- CFS is a heterogeneous group of disorders
- Not all cases are neurological in nature
- Not all cases are post viral
- Immune system abnormalities not universally found
- Overlap with other syndromes including fibromyalgia and primary psychiatric disorders.

World Health Organization Geneva, Switzerland

- Responsible for maintaining ICD, International Code of Diseases.
- Post viral fatigue is classified under diseases of nervous system, G93.3.
- Neurasthenia and fatigue syndromes remain under mental and behavioral disorders, F48.0.
- US is not currently using ICD-10.

Variety of other codes useful to describe symptom related to CFS/ME:
Malaise and fatigue R53.0,
Other malaise 53.81,
Chronic Fatigue unspecified, R53.82,
Unspecified viral encephalitis, A86

Reimbursement not a factor in deliberation of ICD placement.

However, third-party payors and governmental agencies frequently utilize coding to determine coverage and reimbursement policies.

US Governmental Agencies - Approaches to CFS/ME

- Center for Disease Control (CDC)
- National Institute for Health (NIH)
- Trans-NIH
- Department for Human Health
Services (DHHS)

CDC Philosophy

“CFS is a serious illness and poses a dilemma for patients, their families and health care providers”

CDC Basic Facts:

- CFS patients have substantially lower levels of activity. CFS may persist for years.
- The cause has not been identified nor specific diagnostic test available.
- Prevalence of CFS 0.4% or greater than 1 million people in the United States.
- Tens of millions of patients worldwide.

Centers for Disease Control and Prevention; Atlanta, Georgia, 30301

Current position on Chronic Fatigue Syndrome:

Background:

- Acknowledge CFS as serious impairment with unemployment rate of at least 25%.
- Many patients undiagnosed.
- Earlier diagnosis and earlier treatment results in decreased morbidity.
- 40% of population diagnosed with CFS-like symptoms have other treatable disorders.

CDC Case Definition

Introduction

- The 1988 chronic fatigue syndrome (CFS) working case definition (Holmes, et al) did not effectively distinguish CFS from other types of unexplained fatigue. For this reason, it was decided during a 1993 meeting of CFS investigators to develop a logical revision of that definition. The core of the revised CFS case definition is a set of uniformly applicable guidelines for the clinical and research evaluation of CFS and the other forms of fatigue.
- In the revised definition, a consensus viewpoint from many of the leading CFS researchers and clinicians (including input from patient group representatives), chronic fatigue syndrome is treated as a subset of chronic fatigue, a broader category defined as unexplained fatigue of greater than or equal to six month's duration. Chronic fatigue in turn, is treated as a subset of prolonged fatigue, which is defined as fatigue lasting one or more months. The expectation is that scientists will devise epidemiologic studies of populations with prolonged fatigue and chronic fatigue, and search within those populations for illness patterns consistent with CFS.

CDC

Guidelines for the Evaluation and Study of CFS

- A thorough medical history, physical examination, mental status examination, and laboratory tests (diagram) must be conducted to identify underlying or contributing conditions that require treatment. Diagnosis or classification cannot be made without such an evaluation. Clinically evaluated, unexplained chronic fatigue cases can be classified as chronic fatigue syndrome if the patient meets both the following criteria:
- Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial Education in previous levels of occupational, educational, social, or personal activities.
- The concurrent occurrence of 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

- 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 medication.
- Some diagnosable illnesses may relapse or may not have completely resolved during treatment. If the persistence of such a condition could explain the presence of chronic fatigue, and if it cannot be clearly established that the original condition has completely resolved with treatment, then such patients should not be classified as having CFS. Examples of illnesses that can present such a picture include some types of malignancies and chronic cases of hepatitis B or C virus infection.
- 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 bulimia nervosa
- Alcohol or other substance abuse, occurring within 2 years of the onset of chronic fatigue and any time afterwards.

- Severe obesity as defined by a body mass index [body mass index = weight in kilograms ÷ (height in meters)²] equal to or greater than 45. [Note: body mass index values vary considerably among different age groups and populations. No "normal" or "average" range of values can be suggested in a fashion that is meaningful. The range of 45 or greater was selected because it clearly falls within the range of severe obesity.]

Conditions that do not Exclude a Diagnosis of CFS

- Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or melancholic depression, neurasthenia, and multiple chemical sensitivity disorder.
- Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. Such conditions include hypothyroidism for which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels, or asthma in which the adequacy of treatment has been determined by pulmonary function and other testing.
- Any condition, such as Lyme disease or syphilis, that was treated with definitive therapy before development of chronic symptoms.
- Any isolated and unexplained physical examination finding, or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition. Such conditions include an elevated antinuclear antibody titer that is inadequate, without additional laboratory or clinical evidence, to strongly support a diagnosis of a discrete connective tissue disorder.

Diagnostic Criteria I: Chronic Fatigue Syndrome – CDC definition (1988) outline.

The first formal case definition included two major criteria along with the following minor criteria: 6 or more of the symptom criteria listed below and 2 or more of the physical criteria; or 8 or more symptom criteria.

Major criteria:

- New onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person who has no previous history of similar symptoms, that does not resolve with bed rest, and that is severe enough to reduce or impair average daily activity below 50 percent of the patient's premorbid activity level for a period of at least 6 months
- Exclusion of other clinical conditions that may produce similar symptoms (e.g., malignancy, autoimmune disease, chronic psychiatric disease, and chronic inflammatory disease, among others)

Minor criteria:

- Symptom criteria
- Mild fever
- Sore throat
- Painful lymph nodes in the anterior or posterior cervical or axillary distribution
- Unexplained generalized muscle weakness
- Muscle discomfort or myalgia
- Prolonged (\geq 24 hours) generalized fatigue after exercise
- Generalized headaches
- Migratory arthralgia without joint swelling or redness
- Neuropsychologic complaints
- Sleep disturbance
- Physical criteria
- Low-grade fever
- Nonexudative pharyngitis

CFS – British Definition (1990)

- The "Oxford criteria" defined two broad syndromes: chronic fatigue syndrome and post-infectious fatigue syndrome (PIFS). CFS was defined by the following characteristics:
- Fatigue is the principal symptom.
- It is a syndrome of definite onset that is not lifelong.
- Fatigue is severe, disabling, and affects physical and mental functioning.
- Fatigue has been present for a minimum of 6 months, during which it was present for more than 50 percent of the time.
- Other symptoms may be present, particularly myalgia, mood, and sleep disturbance.
- Exclusion criteria included patients with established medical conditions known to produce chronic fatigue and those with certain psychiatric disorders (substance abuse, eating disorders, organic brain disease).

CFS – Australian definition (1990)

- The Australian criteria consisted of the following symptoms:
- Chronic persisting or relapsing fatigue of a generalized nature, exacerbated by minor exercise, causing significant disruption of usual daily activities, and present for more than 6 months
- Neuropsychiatric dysfunction including impairment of concentration evidenced by difficulty in completing mental tasks which were easily accomplished before the onset of the syndrome; new onset of short term memory impairment
- No alternative diagnosis reached by history, physical examination, or investigations over a 6-month period

CDC Criteria (Fukuda 1994)

- Persistent or relapsing fatigue of 6 months or longer in duration
- Other known medical conditions excluded by clinical diagnosis
- Concurrently have the following symptoms:
 - ✓ Impaired memory or concentration
 - ✓ Sore throat
 - ✓ Tender cervical or axillary lymph nodes
 - ✓ Muscle pain
 - ✓ Multi-joint pain
 - ✓ New headaches
 - ✓ Unrefreshing sleep
 - ✓ Post exertional malaise lasting more than 24 hours

CDC definition of Chronic Fatigue (Fukuda 1994)

- Clinically unexplained persistent or relapsing fatigue of new or definite onset which is:
 - Not the result of ongoing exertion
 - Not alleviated by rest
 - Causes substantial reduction in occupational, educational, social or personal activities

The International CFS Definition Revisited (2003)

- The 1988 case definition offered examples of conditions that would preclude a diagnosis of CFS, such as malignancy, autoimmune disease, chronic psychiatric disease, and chronic inflammatory disease. The International Chronic Fatigue Syndrome Study Group elaborated on these exclusionary criteria to include:
- Permanent medical exclusions:
 - Organ failure (e.g., emphysema, cirrhosis, cardiac failure, chronic renal failure)
 - Chronic infections (e.g., AIDS, hepatitis B or C)
 - Rheumatic and chronic inflammatory diseases (e.g., systemic lupus erythematosus, Sjorgren's syndrome, rheumatoid arthritis, inflammatory bowel disease, chronic pancreatitis)
 - Major neurologic diseases (e.g., multiple sclerosis, neuromuscular diseases, epilepsy or other diseases requiring ongoing medication that could cause fatigue, stroke, head injury with residual neurologic deficits)
 - Diseases requiring systemic treatment (e.g., organ or bone marrow transplantation; systemic chemotherapy; radiation of brain, thorax, abdomen, or pelvis)
 - Major endocrine diseases (e.g., hypopituitarism, adrenal insufficiency)
 - Primary sleep disorders (e.g., sleep apnea, narcolepsy)
- Temporary medical exclusions:
 - Conditions discovered at onset or initial evaluation (e.g., effects of medications, sleep deprivation, untreated hypothyroidism, untreated or unstable diabetes mellitus, active infection)
 - Conditions that resolved (e.g., pregnancy until 3 months post-partum, breastfeeding, major surgery until 6 months post-operation, minor surgery until 3 months post-operation, major infections such as sepsis or pneumonia until 3 months post-resolution)
 - Major conditions whose resolution may be unclear for at least 5 years (e.g., myocardial infarction, heart failure)
 - Morbid obesity (body mass index > 40)
- Permanent psychiatric exclusions:
Lifetime diagnoses of bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, dementias of any subtype, organic brain disorders, and alcohol or substance abuse within 2 years before onset of the fatiguing illness

Myalgic Encephalitis/CFS- Canadian Consensus Definition (2003)

- Most widely used by clinicians due to clinical representation of diseases, ease of implementation and treatment guidelines

CFS – CDC

International Definition or Fukuda Definition

- Most widely accepted, currently for research, publication and research design requires compliance with this definition for legitimacy and publication

Canadian Consensus Document (Carruthers, 2003)

- Myalgic Encephalomyelitis / Chronic Fatigue Syndrome:
 - Clinical Working Case Definition
 - Diagnostic and Treatment Protocols

Journal of Chronic Fatigue Syndrome, Vol 11 (1), 2003

Canadian Clinical Working Case Definition of ME/CFS

A patient with ME/CFS will meet

Criteria

The criteria for:

- Fatigue, post-exertional malaise, and/or fatigue, sleep dysfunction and pain
 - Have two or more neurological/cognitive more symptoms from two of the categories of autonomic, neuroendocrine, and immune manifestations
 - Adhere to item 7
1. Fatigue
 2. Post-exertional malaise and/or fatigue
 3. Sleep dysfunction
 4. Pain
 5. Neurological/cognitive manifestations (two or more)
 6. At least one symptom from two of the following categories:
 1. Autonomic manifestations
 2. Neuroendocrine manifestations
 3. Immune manifestations
 7. Illness that persists for at least six months and has a distinct onset (although onset may have been gradual)

Neurological/Cognitive Manifestations

Two or more of the following:

- Confusion
- Impairment of concentration and short- term memory consolidation
- Difficulty with information
- Disorientation
- Perceptual and sensory disturbances
- Ataxia
- Muscle Weakness
- Fasciculation
- Overload phenomena: cognitive, sensory and emotional

1. Fatigue

- Significant degree of physical and mental fatigue
 - New onset
 - Unexplained
 - Persistent
 - Recurrent
- Fatigue substantially reduces activity level



2. Post-Exertional Malaise and/or Fatigue

- Inappropriate loss of physical and mental stamina
- Rapid muscular and cognitive fatigability
- Post exertional malaise and/or fatigue and/or pain
- Tendency for other association symptoms to worsen
- Pathologically slow recovery period – usually 24 hours or longer

3. Sleep Dysfunction

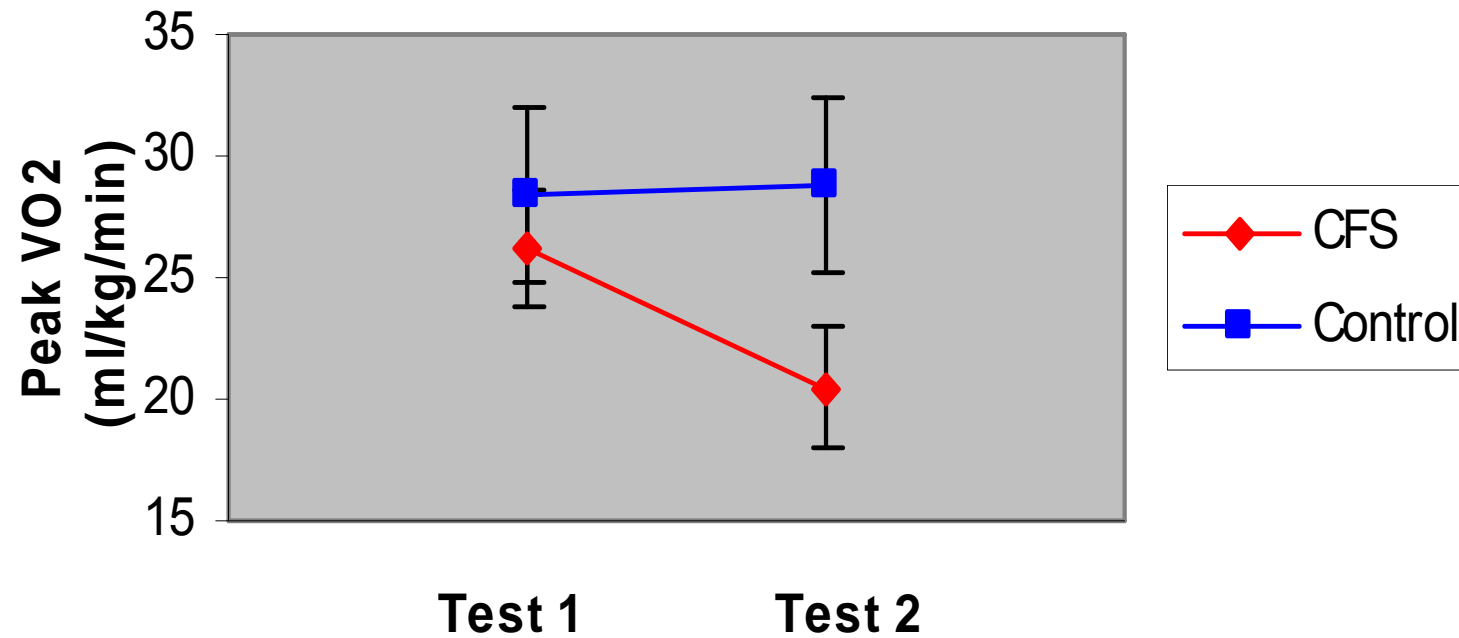
- Unrefreshed sleep, or
- Sleep quantity, or
- Rhythm disturbances, such as reversed or chaotic diurnal sleep rhythms

A small number of patients have no sleep dysfunction, but no other diagnosis fits except ME/CFS

Aerobic Energy System Compromised

- Aerobic Impairment
- Reduced Functional Capacity
- Link to Immune Dysfunction

Oxidative Impairment in the Post-Exertional State



4. Pain

- Significant degree of myalgia
- Pain in the muscles and/or joints, often widespread and migratory in nature
- Significant headaches of new type, pattern, or severity

A small number of patients have no pain, but no other diagnosis fits except ME/CFS

5. Other Symptoms

Autonomic Manifestations

- Orthostatic intolerance-neurally mediated hypotension (NMH)
- Delayed postural hypotension
- Light-headedness
- Extreme pallor
- Nausea and irritable bowel syndrome
- Urinary frequency and bladder dysfunction
- Palpitations with or without cardiac arrhythmias
- Exertional dyspnea

Neuroendocrine Manifestations

- Loss of thermostatic stability
- Marked weight change
- Loss of adaptability and worsening of symptoms with stress

Immune Manifestations

- Tender lymph nodes
- Recurrent sore throat
- Recurrent flu-like symptoms
- General malaise
- New sensitivities to food, medications, and/or chemicals

6. Illness Duration

- Illness persists for at least 6 months
- Usually a distinct onset, although it may be gradual
- (Preliminary diagnosis may be possible earlier than 6 months)
- (Illness duration of 3 months is appropriate for children)

Some patients may have been unhealthy for other reasons prior to onset of ME/CFS and lack detectable triggers, and/or have more gradual or insidious onset

NATIONAL INSTITUTES OF HEALTH
Nation's Medical Research Agency

DHHS Advisory Committee, Department of Health and Human Services, Chronic Fatigue Syndrome Advisory Committee

- Established in 1996 to advise Department of Health and Human Services on policy with respect to Chronic Fatigue Syndrome.
- Brought together officials representing health agencies and seven appointed members of the public.
- Established Chronic Fatigue Syndrome Advisory Committee. Current membership: Biomedical researchers 7, disability and clinical care expertise patient advocates 4.
- Agencies represented:
 - National Institute of Health (NIH),
 - Centers for Disease Control and Prevention (CDC),
 - Food and Drug Administration (FDA),
 - Health Resources and Services Administration (HRSA),
 - Social Security Administration (SSA)

Chronic Fatigue Syndrome Advisory Committee (CFSAC)

- Hold meetings
- Activities:
 - has addressed expansion of CSF biomedical research
 - appropriate name change for the syndrome
 - pediatric CFS
 - disability
 - health provider education

Trans-NIH working group on Chronic Fatigue Syndrome

(Office of Research on Women's Health-ORWH)

Diagnostic Criteria

Introduction: CFS is a clinically diagnosable condition with well-documented history.

- Symptoms of CFS are variable in severity and not homogenous making acceptable research in clinical diagnostic criteria difficult

Leadership IACFS/ME

Board of Directors

- David S. Bell, MD / Editor
- Lucinda Bateman, MD / Secretary
- Brigitta Evengård, MD, PhD / Vice-President
- Leonard A. Jason, PhD /Vice President, ex-officio
- Nancy G. Klimas, MD / President
- Hirohiko Kuratsune, MD, D. Med Sci / Chairperson, Internat'l Cmttee
- Kenneth Friedman, PhD / Chairperson, Membership Cmttee
- Lee B. Meisel, MD, J.D. / Chairperson, Website Cmttee
- Fred Friedberg, PhD / Treasurer
- Gudrun Lange, PhD / Chairperson, Journal Cmttee

IACFS is in the developmental phase of treatment guidelines using their board members and outside consultative opinion

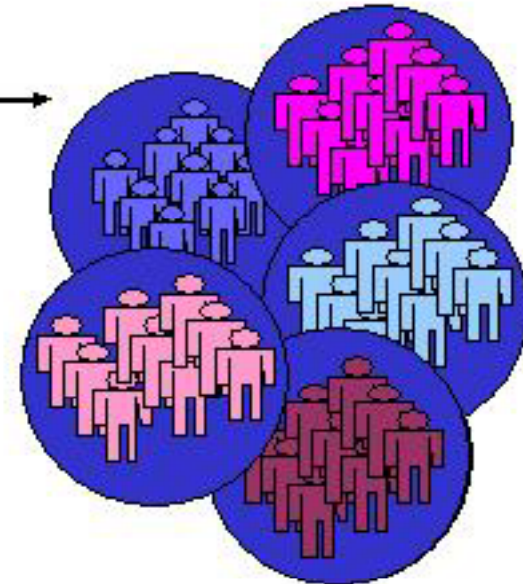
Subsets of CFS/ME

Gene Expression Differentiates Subgroups of People with CFS

Fatigue



1. **Vac14**: regulates phosphatidylinositol kinases (stress response and membrane trafficking)
2. **SLC1A6**: an excitatory aa transporter (glutamate/aspartate)
3. **Fbxo7**: Fbxo7 has been characterised as a selective enhancer of cdk6 activity (regulate major cell cycle transitions)
4. **ZNF350**: crucial roles in ubiquitination events involved in diverse cellular processes including signal transduction (MAPK), differentiation and apoptosis



1. **PTCH2**: receptor for shh signaling which is active in T cell growth and differentiation and proliferation
2. **TCL1A**: TCL1A regulates the growth and survival of peripheral T cells

Brain SPECT Scans: Regional Hypoperfusion

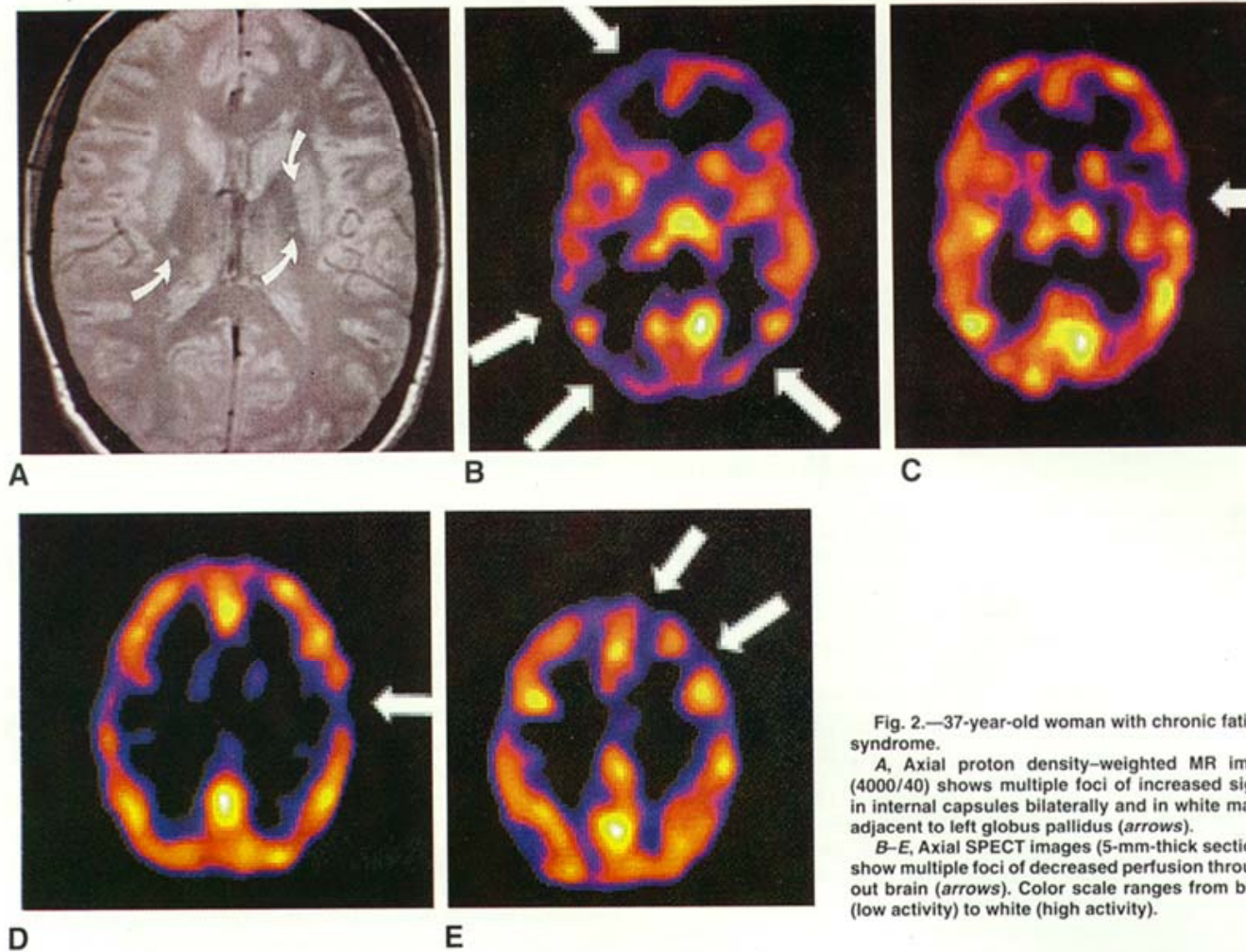


Fig. 2.—37-year-old woman with chronic fatigue syndrome.

A, Axial proton density-weighted MR image (4000/40) shows multiple foci of increased signal in internal capsules bilaterally and in white matter adjacent to left globus pallidus (arrows).

B–E, Axial SPECT images (5-mm-thick sections) show multiple foci of decreased perfusion throughout brain (arrows). Color scale ranges from black (low activity) to white (high activity).

Model of CFS Pathogenesis

Genetic Predisposition



Triggering event / infection



Mediators (Immune, endocrine, neuroendocrine, psychosocial, viral reactivation or persistence)



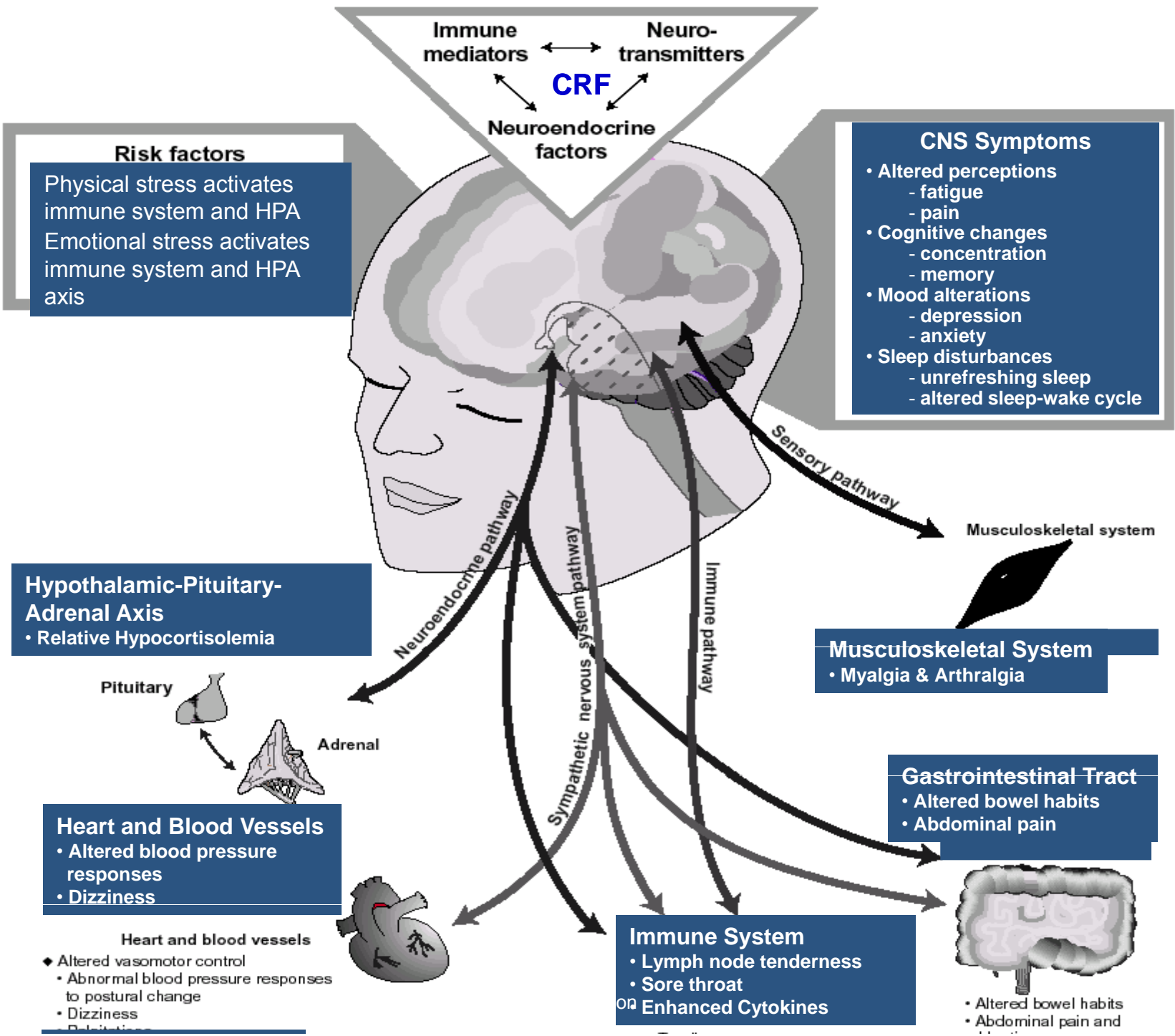
CFS/ME

Genetic Predisposition - CFS

- HLA DR haplotypes in 112 South Florida CFS patients, compared to 5,000 regional and national controls
- 4 to 6 fold increased relative risk for DR4, DR3 and DQ3. (Keller et al, 1992)
- Seattle CFS Cooperative Research Center Twin study - genetic predisposition, heritability estimate of 51% (2nd World Conf); similar results in Sweden, Australian studies

Evidence for Triggering event/ infection - CFS

- 60 to 80% of CFS subjects date the onset of their illness to an acute viral-like illness (Komaroff, Buchwald) Less so in population based studies. (Reeves, Jason)
- Andrew Lloyd and colleagues in Australia performed a prospective study during and after acute EBV, Q fever or Ross River Virus - Anergy during acute infection predicted persistent CFS like symptoms
 - Severity of initial infection single best predictor

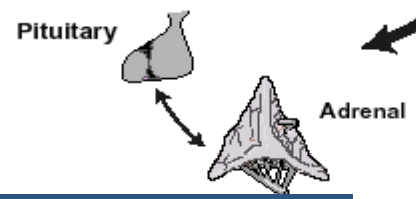


Risk factors
 Physical stress activates immune system and HPA
 Emotional stress activates immune system and HPA axis

CNS Symptoms

- Altered perceptions
 - fatigue
 - pain
- Cognitive changes
 - concentration
 - memory
- Mood alterations
 - depression
 - anxiety
- Sleep disturbances
 - unrefreshing sleep
 - altered sleep-wake cycle

Hypothalamic-Pituitary-Adrenal Axis
 • Relative Hypocortisolemia



Heart and Blood Vessels
 • Altered blood pressure responses
 • Dizziness

Heart and blood vessels

- ◆ Altered vasomotor control
- Abnormal blood pressure responses to postural change
- Dizziness

Musculoskeletal System
 • Myalgia & Arthralgia

Gastrointestinal Tract
 • Altered bowel habits
 • Abdominal pain

Immune System
 • Lymph node tenderness
 • Sore throat
 • Enhanced Cytokines

Gastrointestinal Tract
 • Altered bowel habits
 • Abdominal pain and

Research

Historical Infectious Agents Associated with ME/ CFS

Background

- Infectious agents may trigger and perpetuate CFS.
- Pathogens associated with CFS have in common that they are difficult or impossible for the immune system to eliminate.
- Human herpes viruses associated with CFS include:
HHV4 (EBV), HHV6 and HHV7.
- Other associated infectious agents include: parvovirus B19, enteroviruses, *Borrelia burgdorferi*, and *mycoplasma fermentans*.

Research The Task

- Determine viral reservoirs in ME/CFS patients.
- Determine the state of viral expression in various patient tissues compartments.
- Identify subgroups of ME/CFS by cytokine/chemokine profiling.
- Further investigate the previously reported presence of clonal TCR γ rearrangements in CFS/ME patients.

- Outbreaks of CFS suggest a role for pathogens in the initiation or progression of the disease for example, 'Royal Free disease', 'epidemic neuromyasthenia', etc. In the Royal Free Hospital outbreak in 1955, 292 medical, nursing, ancillary and administrative staff were affected. Another well documented CFS outbreak occurred in Los Angeles in 1934 (Dawson J. BMJ 1987; 294:327-8).

- The disease also occurs in an edemic fashion. In addition, Henderson and Shelokov, reported an outbreak in punta Gorda Florida in 1959; Grufferman et al. noted 4 cases of cancer associated with an outbreak of fatigue involving the North Carolina Orchestra. Low natural killer cell activity was found in this cohort. Interestingly, two of the four tumors were non-Hodgkin's lymphoma and brain cancer. A number of other reports of outbreaks have followed (Holmes, Kaplan et al., 1987; Bell and Bell 1988).

- The outbreak in Incline Village has been supported by outside investigators as reported by Holmes et al (CDC) in JAMA and Levine et al (NIH) in the Archives of Int Med (ref).
- No etiologic agent was identified for most of these outbreaks although two W. Otago, NZ and Placerville, CA coincided with an excess of giardiasis.
- Thus, outbreaks of CFS are known to occur and are likely to be due to a variety of transmissible agents, and so the possibility remains that a novel retrovirus or other infectious agent could be involved.

Overview of Viruses and Chronic Fatigue Syndrome

- **Mesh heading search in the National Library of Medicine for years 1997-2007**
 - **Mesh headings: fatigue syndrome, chronic and viruses**
 - **Assessed only papers that compared viral infections in populations of CFS patients and healthy control subjects**
 - **Major viral candidates:**
 - HHV-6 (3 of 7 papers supportive)
 - HCMV (2 of 5 papers supportive)
 - EBV (2 of 4 papers supportive)
 - HHV-7 (1 of 4 papers supportive)
 - Enteroviruses (2 of 2 papers supportive) [tissues]
 - Parvoviruses (B19) (1 of 2 papers supportive)

Characteristics of the Human Herpesvirus Family

General Properties

- Three subfamilies are recognized, designated alpha (HSV1, HSV2, VZV), beta (CMV, HHV-6, HHV-7) and gamma (EBV, HHV-8).
- First infections usually occur in childhood, and seroprevalence is high (> 50% in adults) for all herpesviruses except HHV-8.
- In virtually all cases lifelong latent infections are established.
- Reactivations of the viruses from latency are common.
- Minority of people suffer clinical illness, sometimes severe, as a result of herpesvirus reactivations. Chronic, active infections are sometimes established.

Natural History of Primary HHV-6 Infections

Natural History of Primary HHV-6 Infection

Exanthem Subitum

- First described by Zahorsky in 1910
- Characterized by high fever for several days
- Maculopapular rash occurs in 10% to 40% of cases
- HHV-6 shown to be causative agent in 1988
- >90% of children infected by two years of age

Active HHV-6 Infections in Patients with Chronic Fatigue Syndrome and Relapsing-Remitting MS

Comparative Study of HHV-6 Infections in Patients with CFS and Relapsing-Remitting MS

- *Why compare multiple sclerosis and chronic fatigue syndrome?*
- Both are chronic, debilitating diseases
- Both have important fatigue components
- Both involve significant neurocognitive impairments
- Both may be triggered and/or perpetuated by a viral infection

Methods for the Diagnosis of Human Herpesvirus Six Infections

*Diagnostic Methods Used By
Wisconsin Viral Research Group*

- Nested HHV-6 Plasma PCR
- Immediate Early Protein Specific Antigenemia
- Rapid HHV-6 Culture

•KKnox, DCarrigan, Wisconsin Viral Research

Natural History of Primary HHV-6 Infection

Summary: Clinical Manifestations

- Bone marrow suppression
- CD4+ T lymphopenia
- Encephalitis
- Acute pneumonitis

A and B Variants of HHV-6

Epidemiology of HHV-6 Variant

A

- Roseola (exanthem subitum) is HHV-6 variant B
- <2% HHV-6 variant A by age of two years
- 44% HHV-6 variant A as primary infections in Uganda
- Approximately 10% HHV-6 variant A by age of 12 years in USA
- 71% HHV-6 variant A in normal lung tissues in USA

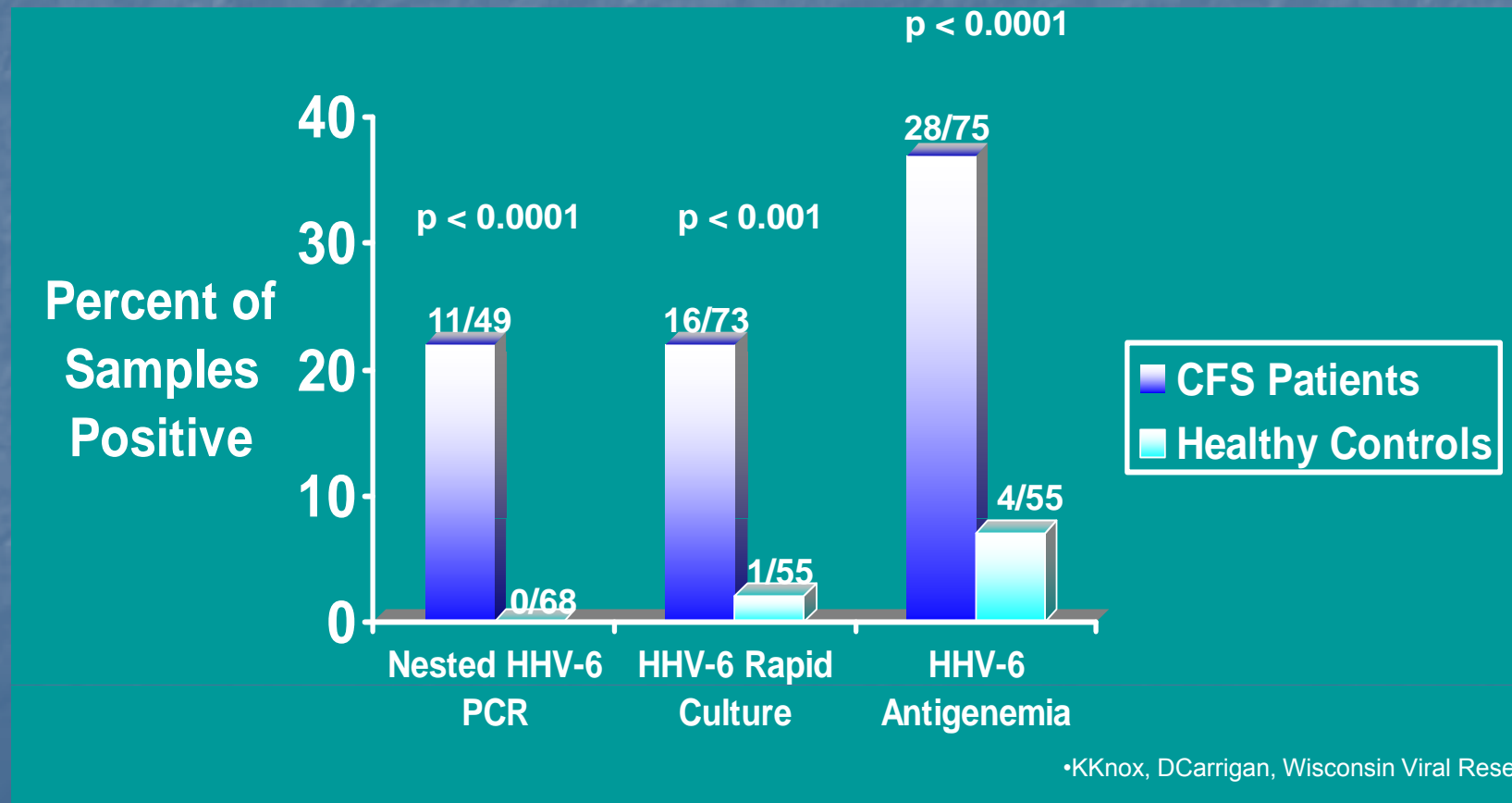
A and B Variants of Human Herpesvirus Six

Comparison of Biologic Properties of HHV-6A and HHV-6B

- Overall, nucleotide sequence identity between HHV-6A and HHV-6B is 90%
- Nucleotide sequence divergence between HHV-6A and HHV-6B clusters in immediate early/regulatory genes
- HHV-6A is able to infect and completely replicate in more cell types than HHV-6B, including macrophages and NK cells
- HHV-6A but not HHV-6B induces high level production of TNF α in blood and bone marrow leukocytes

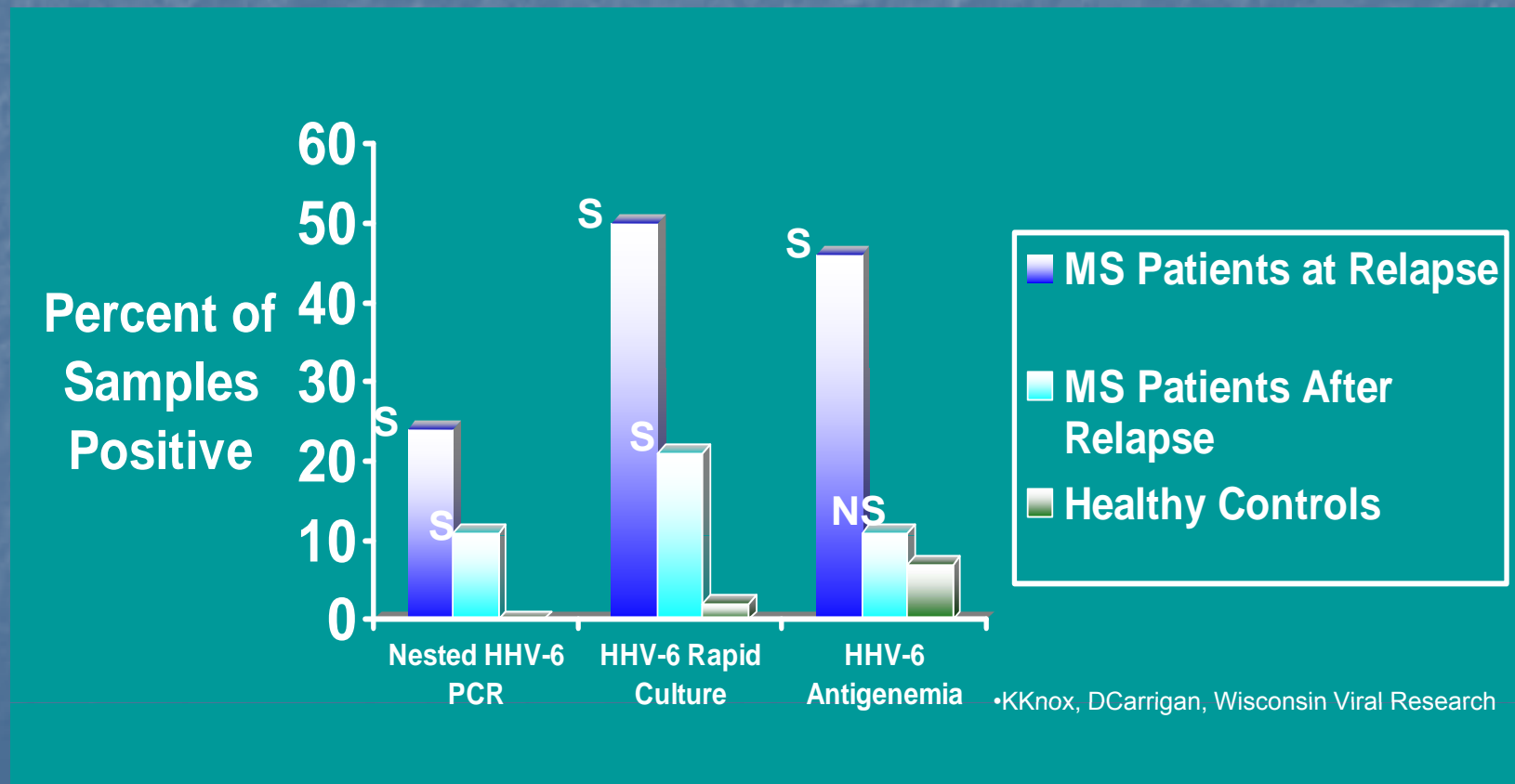
Detection of HHV-6 Infections In Patients with CFS and Healthy Controls

Comparison of Testing Methodologies Using Cross Sectional Blood Samples



Detection of HHV-6 Infections In Patients with MS and Healthy Controls

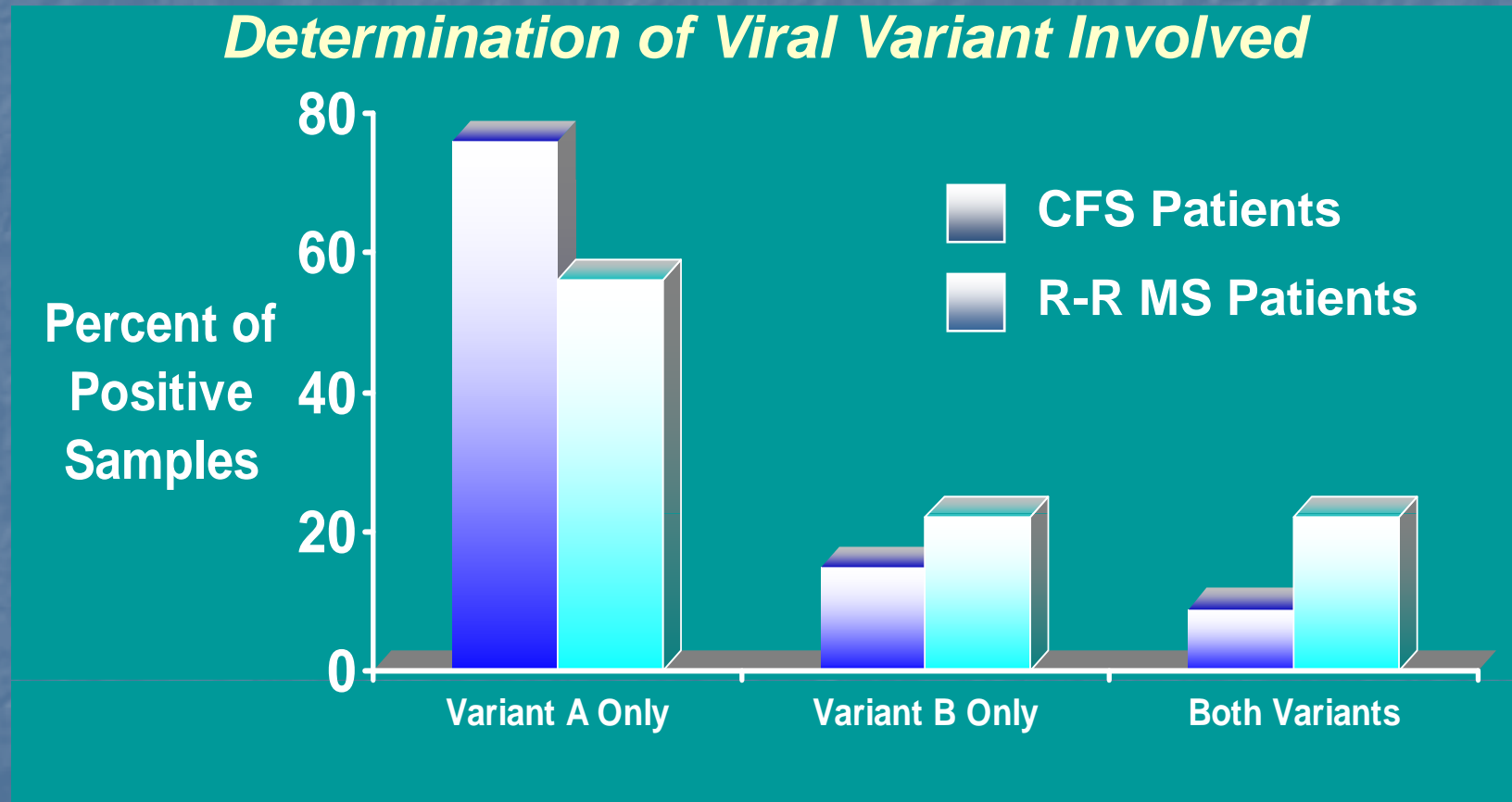
Comparison of Testing Methodologies Using Cross Sectional Blood Samples



•KKnox, DCarrigan, Wisconsin Viral Research

S: Significant difference compared to controls — NS: Not significantly different from controls

Detection of HHV-6 DNA In Plasma Samples from CFS and MS Patients by Nested PCR



Comparative Study of HHV-6 Infections in Patients with CFS and Relapsing-Remitting MS

Why compare multiple sclerosis and chronic fatigue syndrome?

- Both are chronic, debilitating diseases
- Both have important fatigue components Both involve significant neurocognitive impairments
- Both may be triggered and/or perpetuated by a viral infection

Post-Infectious Fatigue Syndrome (PIFS)

- In 2006, a landmark study of post-infectious fatigue syndrome that was conducted in Dubbo, Australia, was published. The team studied people with each of three different kinds of infections – Epstein-Barr virus infection, Ross River virus infection, and infection with a bacterium, *Coxiella burnetii*, the cause of a disease called Q fever. The study showed that about 10% of patients in each of the three groups developed a post-infectious fatigue syndrome that met the Centers for Disease Control and Prevention (CDC) criteria for CFS.

Epstein-Barr Virus

- Proteins made by EBV during active infection stimulates the production of several cytokines.
- These cytokines can produce many symptoms of CFS

Parvovirus

- Japanese research followed 200 patients immediately after being infected with virus.
- PIFS not associated with continued presence of viral DNA in blood but rather levels of complement-proteins involved in inflammation.

Enteroviruses

- Includes 3 families of human viruses: Coxsackievirus, echovirus and poliovirus
- These infect cells of brain and spine cord, respiratory tract, muscle and gut cells.
- Have been suspected as possible cause of CFS for decades.

Borna disease virus

- Infects horses, cattle, dogs and cats.
- Causes infection of the brain in humans, particularly limbic system which is involved in emotion, behavior, and long-term memory.
- A German team reported it had isolated Borna disease virus from blood of patient with CFS.
- Team in Japan reported Borna disease virus in 10% of CFS patients.

Endogenous retrovirus

- Researchers reported a particular endogenous retrovirus called human endogenous retrovirus-K-18 (HERV –K18) can be induced to make viruses when cell is infected with DBV or stimulated by a chemical called interferon- α (which is both a natural chemical and a drug used in various treatments).
- 3 different variants of HERV-K18 exist
- The team reported 1 variant, K18.3, is found more often in patient with CFS.
- The possibility that HERV-K18 might trigger CFS is plausible: HERV-K18 makes a protein called a 'superantigen' that triggers a strong immune response and dysregulates the immune system.
- Such a response could theoretically trigger the symptoms of CFS.
- Although preliminary research, it is intriguing.

- Several studies have reported an increased incidence of tumorigenesis in CFS patients and this is likely to be closely linked to herpes virus infections. One such study reported an increased incidence of primary brain and lymphoid tumors in CFS patients followed longitudinally (Levine, Fears et al. 1998). Herpes viruses have been associated with lymphoma by a variety of mechanism including virus gene integration and viral co-activation (Gruss and Kadin 1996).

Viral Infections In Patients with CFS

Summary

- Patients with CFS appear to have increased vulnerability to viral infections, especially from members of herpesvirus family.
- Vulnerability may be due to increase in viral burden as result of poor immune surveillance: defects in NKC function and IFN response pathway.
- Patients may suffer specific antiviral defects: STAT-1 deficiency resulting in failure of T-lymphocyte to response to gIFN, and HHV-6 infection and destruction of immune cells.

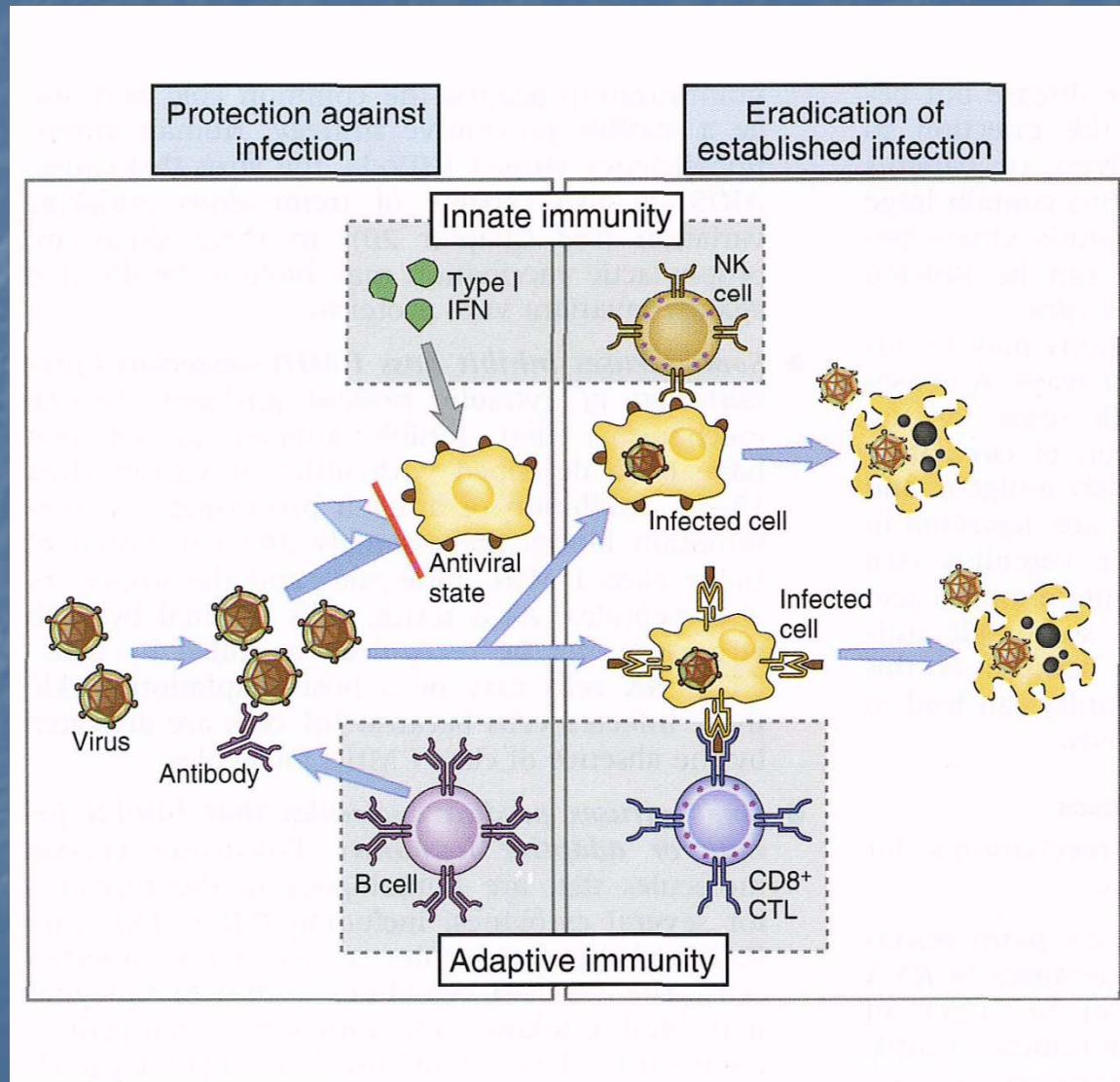
Treatment

Current Options for Treating Viral Infections

- Foscarnet FOSCAVIR
- Valganciclovir VALCYTE
- Ganciclovir CYTOVENE
- Acyclovir ZOVIRAX
- Valcyclovir VALTREX (Acyclovir prodrug)
- Cedofovir VISTIDE or (S)-HPMPC
- Poly I PolyC12U AMPLIGEN
(approved in Canada only)

**Do patients with CFS
have immunologic
defects that make them
vulnerable to viral
infections?**

Immune Responses to Viruses



Differences in TH1, TH2 and TH17 Functional T-cell subsets in ME/CFS patients vs healthy Controls

FUNCTIONAL T-CELLS				
	Cytokine	Patient N = 90	Control N=121	Function
TH ₁	IL-2	150	27	Stimulates growth and differentiation of T cell response
	IFN- γ	18	12	Antiviral
	IL-12	306	211	Differentiation into Cytotoxic T cells with IL-2
TH ₂	IL-4	26	49	Proliferation
	IL-5	4	11	Production, differentiation, IgA production
	IL-13	76	86	Inhibits TH1-cells and the production of macrophage inflammatory cytokines
	IL-10	49	19	Inhibits Th1 cytokine production
	IL-13	76	86	Stimulates growth and differentiation of B-Cells
T _{reg}	CD-25	332	516	Immunosuppressive
TH ₁₇	IL-17	29	57	Osteoclastogenesis, angiogenesis
	IL-6	1525	29	Induces acute phase reaction, hematopoiesis, differentiation, inflammation

Mean values in pg/mL. Red denotes upregulation, Blue denotes downregulation



Differences in Pro-inflammatory Cytokines in CFS and Controls

PROINFLAMMATORY CYTOKINES			
Chemokine	Patient N = 90	Control N=121	Function
IFN- α	68	63	Type I, expressed by all cells to stimulate both macrophages and NK cells to elicit an anti-viral response, anti-tumor
IFN- γ	18	12	Type II, antiviral, secreted by T lymphocytes, dendritic cells and NK cells, immunoregulatory, and anti-tumour
GM-CSF	212	161	Stimulates stem cells to produce granulocytes and monocytes, part of the immune/inflammatory cascade
IL-7	73	76	Hematopoietic growth factor, B and T cell development
IL-1Rα	1392	284	Inflammatory response against infection, re-set the hypothalamus thermoregulatory center, increased body temperature
IL-1β	201	86	
TNFα	226	71	Extrinsic pathway for triggering apoptosis
IL-10	96	46	Anti-inflammatory, block NF- κ B activity



Several Inflammatory Chemokines previously linked to chronic inflammatory diseases are upregulated in ME/CFS vs. Controls

INFLAMMATORY CHEMOKINES				
	Chemokine	Patient N = 90	Control N=121	Function
CXC	IL-8	2034	10	Neutrophil Chemotactic Factor
	MIG	79	83	T-cell chemoattractant induced by IFN- γ
	IP-10	145	30	Chemoattraction for monocytes and T cells
CC	MCP-1	587	441	Recruitment of monocytes, T lymphocytes, eosinophils, basophils
	MIP-1α	1371	78	Acute inflammatory state in the recruitment and activation of polymorphonuclear leukocytes
	MIP-1β	3400	174	Activate human granulocytes (neutrophils, eosinophils and basophils) which can lead to acute neutrophilic inflammation
	RANTES	33251	9287	Chemotactic for T cells, eosinophils, and basophils, active role in recruiting leukocytes into inflammatory sites
	EOTAXIN	271	91	Recruits eosinophils by inducing their chemotaxis

Mean values in pg/mL. Red denotes upregulation, Blue denotes downregulation

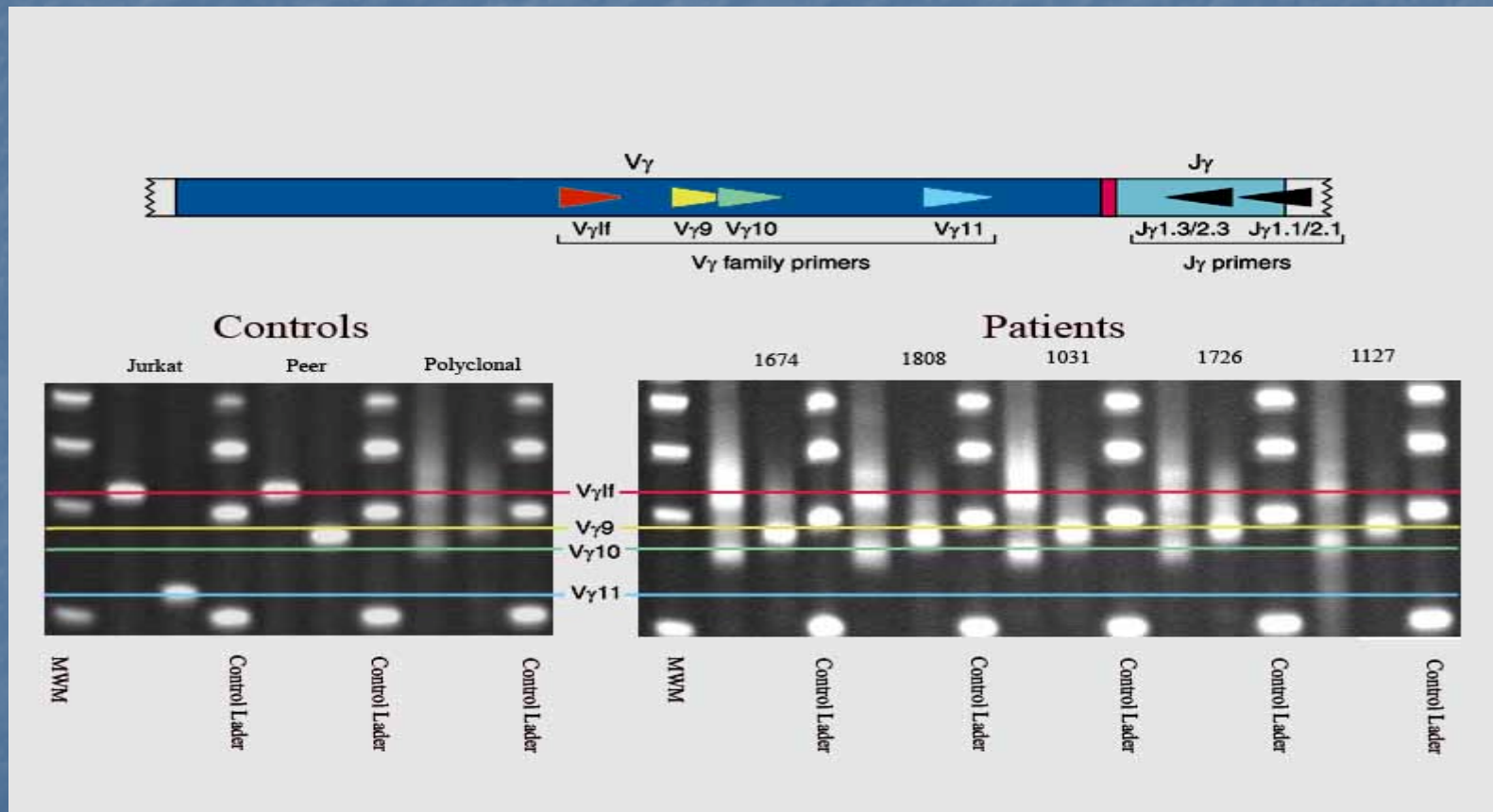


TCR γ Rearrangement Testing in Nevada CFS/ME Cohort

- Criteria for Testing:
 - Acute (viral) onset of CFS/ME
 - Lymphadenopathy and/or splenomegaly
 - 170 CFS patients tested
- Results:
 - 59 positive for mono clonality
 - 59 TCR γ
 - 4 TCR γ + IGH
 - 1 IGH alone



TCR γ Clonality in Nevada CFS/ME Cohort

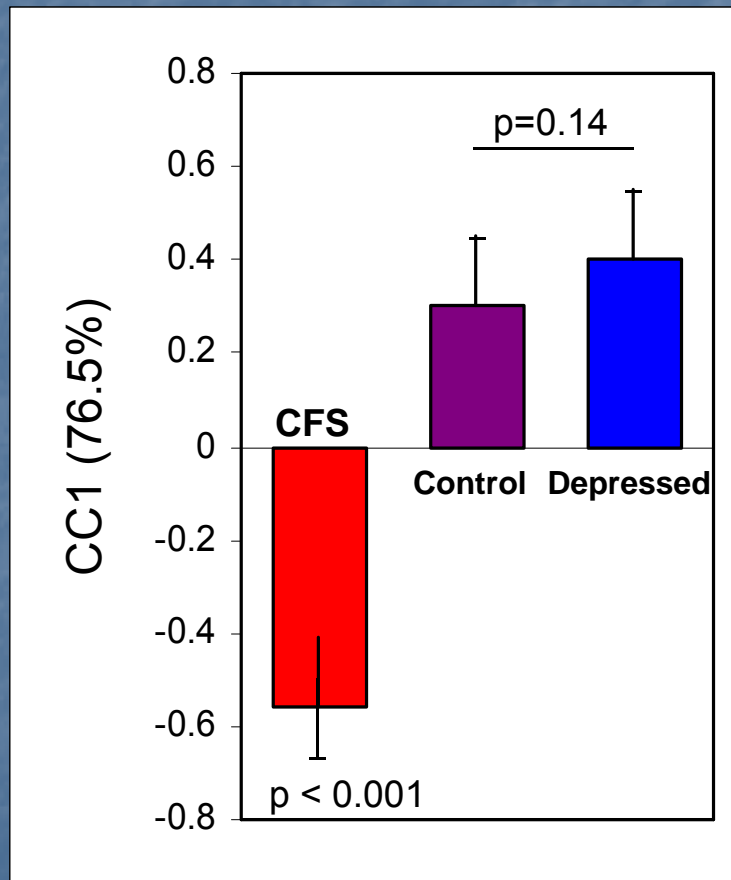


Summary of virus associations and development of clonal TCR γ rearrangements

Nevada CFS Cohort	HHV6	HHV6 Strain A	HHV6 Strain B	T-Cell Clonality	NHL in TCR γ patients	TCR γ in NHL Patients
% Positive	254/540 47%	71/254 28%	43/254 17%	59/170 Tested 35%	11/59 TCR with NHL 19%	11/19 NHL have T-Cell Clonality 58%



Results: Immune function multivariate analysis



Multivariate Analysis included:

- 37 kDa RNase L
- RNase L activity
- Bioactive 2-5A
- Interferon- α
- NK %
- NK activity

- It has been reported a significant incidence of CFS patients demonstrate monoclonal TCR γ rearrangements and active HHV6 infections and cancer^{1,2};

- Importantly, the rearrangements and tumors are manifested in a younger population harboring other immunological defects including reduced NK cell function and RNase L activity

Suggesting a correlation between long term expression of viruses such as HHV6 and EBV and chronic immune stimulation resulting in immune dysfunction and cancer.

1 Vrsalovic, Korac et al 2004

2 Peterson, Knox et al 2006

Evidence for Dysregulation of Antiviral Pathway in Patients with CFS

- **Natural killer cells:
Involved in viral and tumor cell surveillance**

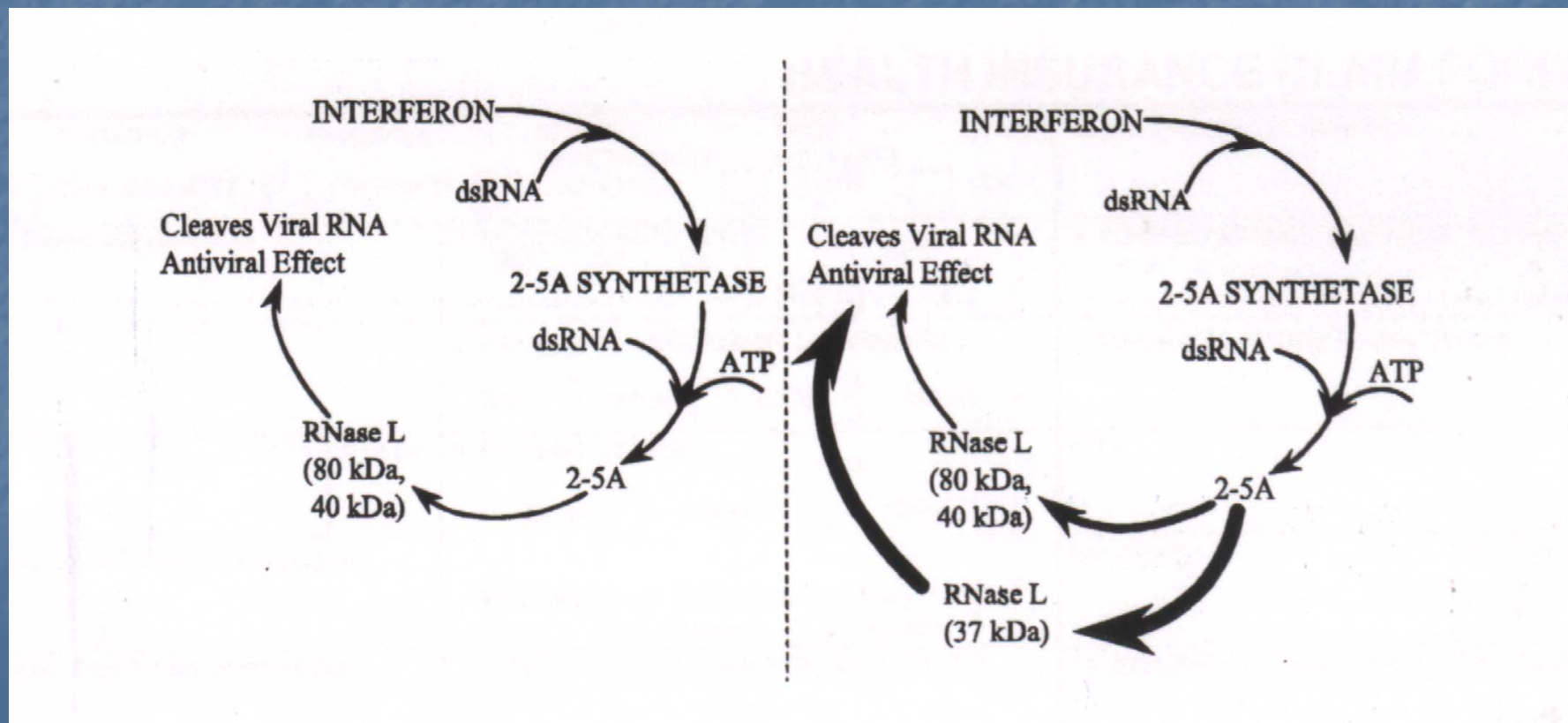
Consistent evidence of impaired cytolytic activity in CFS patients

- **Interferon response pathway
i.e. the 2-5A/RNase L/STAT1 pathway**

Consistent evidence for degradation of RNase L and abnormally low STAT1 levels in patients with CFS

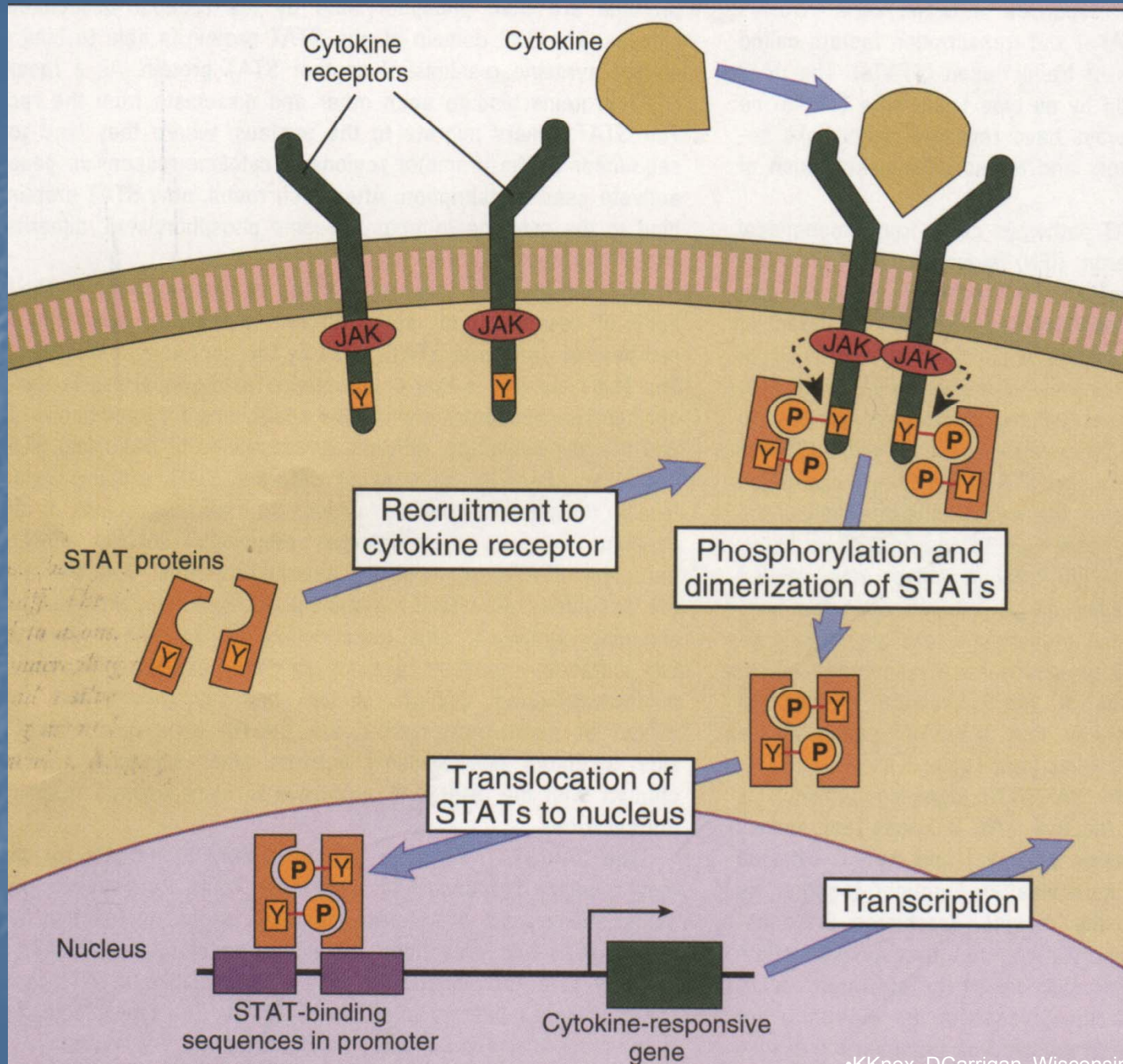
Importance of STAT1 in CFS stems from recent observations suggesting that Type 1 interferon responses are abnormal in many patients with CFS

review by AL Komaroff; Amer J Med 108:169 (2000)



STAT1

- Centrally involved in the response of cells to
 - Type 1 interferons (alpha and beta)
 - Type 2 interferon (gamma)
- In both animals and humans, defects in STAT1 are associated with fatal infections by both viruses and bacteria.



Two-Sided Fisher's Exact Test Analysis of STAT1-91/84 Expression in Healthy Control Subjects and CFS Patients

	Healthy Controls	CFS Patients	Total
STAT1-91/84 Negative	1 (4%)	8 (32%)	9
STAT1-91/84 Positive	26 (96%)	17 (68%)	43
Total	27 (100%)	25 (100%)	52

p = 0.0098; Very Significant

WVRG Study of STAT1 Protein Expression in CFS Patients

Conclusions

- STAT1 is comprised of at least five antigenically related proteins with the two most fully studied being the STAT1-91 (alpha splicing variant) and STAT1-84 (beta splicing variant).
- A subset (approximately 30%) of patients with CFS have a quantitative deficiency in the expression of STAT1-91/84 proteins.
- This deficiency may predispose the patients to develop a variety of infections due to dysfunction of the type 1 and type 2 interferon systems.

Viral Infections In Patients with CFS

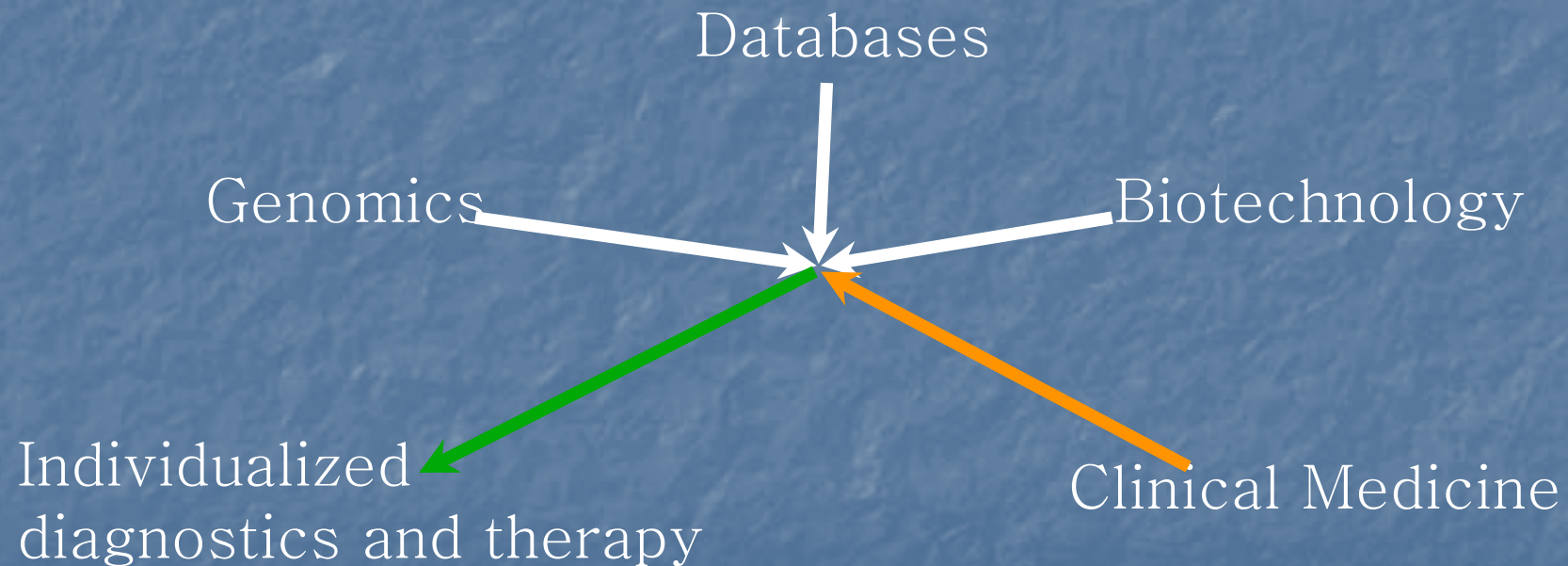
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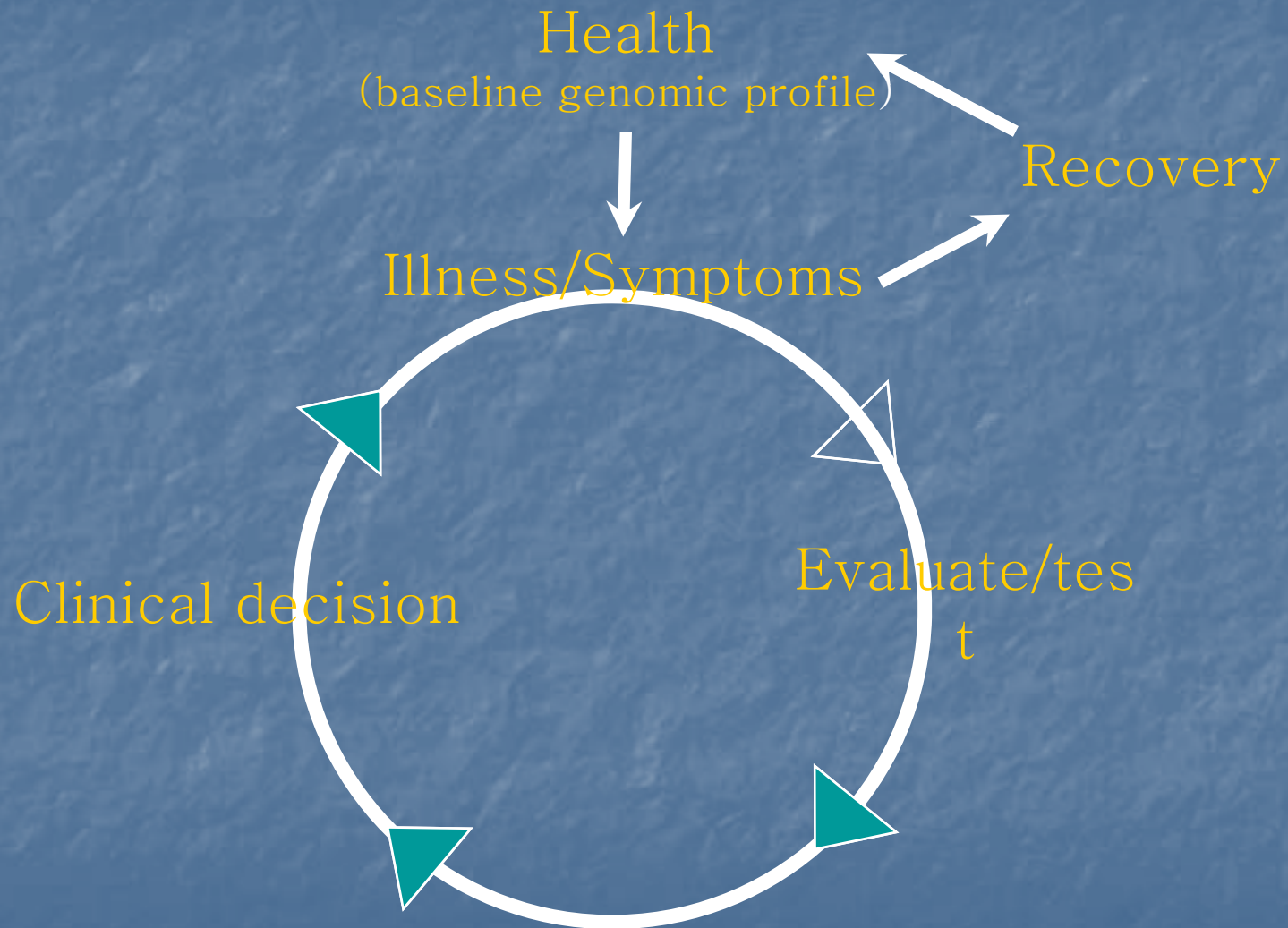
Overview of Informatics

- Applications
 - Host-response signatures
 - Informatics-based surveillance
 - Clinical trials and therapeutic monitoring
 - Utilizing large-scale databases and genomic nosologies

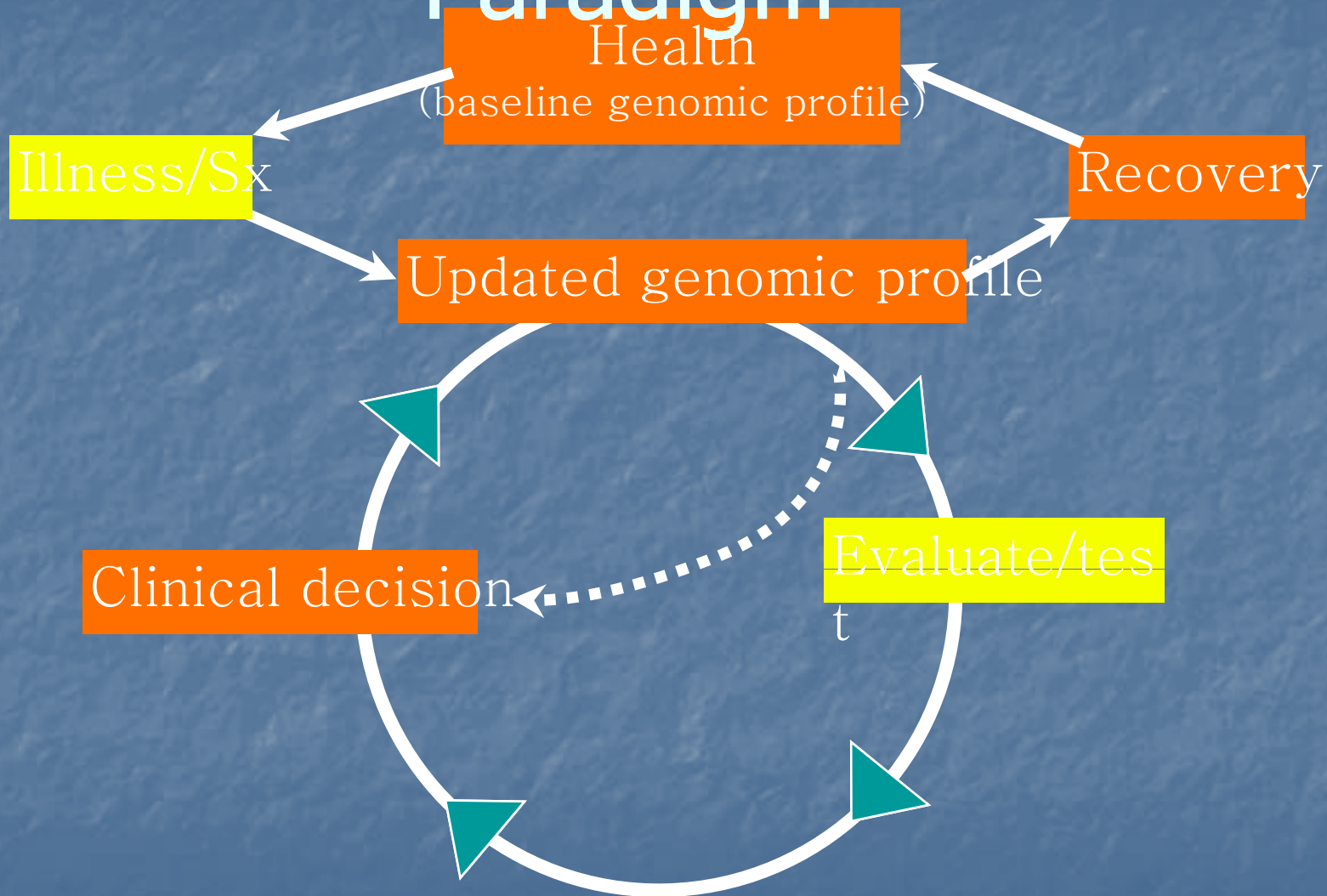
Informatics new paradigm: Convergence



Clinical Care Paradigm



Improved Clinical Care Paradigm



Neuroimmune Institute Mission

Comprehensive Evaluation, Treatment, and Research



National Concerns:

- Practitioner and patient-based demand for evidence-based guidelines for provider education
- 3500 publications without clear-cut guidelines
- Few recognized experts
- Few complete data sets

Failure to diagnose:

- Estimated 80% of CFS/ME are undiagnosed or self diagnosed. The patients were unable to find expert providers
- Inadequate training of MDs remains the largest obstacle for patients
- Models for other diseases with respect to diagnostic and treatment algorithms.

WPI Rationale

- One in 300 US citizens suffers from ME/CFS
- One in 750 suffers from MS
- One in 158 boys suffers from autism
- One in 150 suffers from fibromyalgia
- Neuro Immune diseases are on the rise



Our Mission

- To facilitate and advance patient care
- Research the pathophysiology of neuro-immune diseases
- Develop therapeutics, diagnostics and prevention strategies for this spectrum of diseases



A Unique “Center of Excellence” Model

- A comprehensive outpatient medical and translational research center dedicated to: patient care, basic research, education and drug development for a spectrum of neuro-immune diseases.
- A ‘First of its Kind” Institute dedicated to Neuro-Immune Disease. Integrating: patient treatment, basic and clinical research, and medical education.



Current WPI Research

- Gene expression profiling on ME/CFS
- Virus expression profiling in CFS
- Clonal T cell receptor gamma rearrangements and MCL development
- Chromosomally integrated HHV6 (CI HHV6)
- Cytokine and proteomic profiles by antibody array

- We welcome collaboration with similar institutes, health care organizations, and government bodies internationally including Sweden and the Scandinavian countries.

