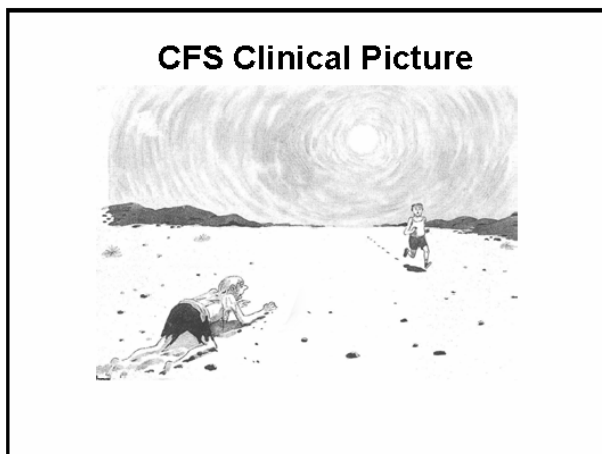
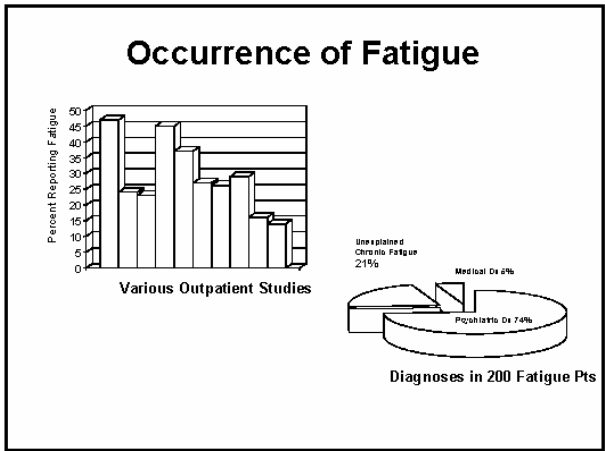


Presentation 4- William Reeves

Chronic Fatigue Syndrome

Occurrence, Case Definition, Pathophysiology

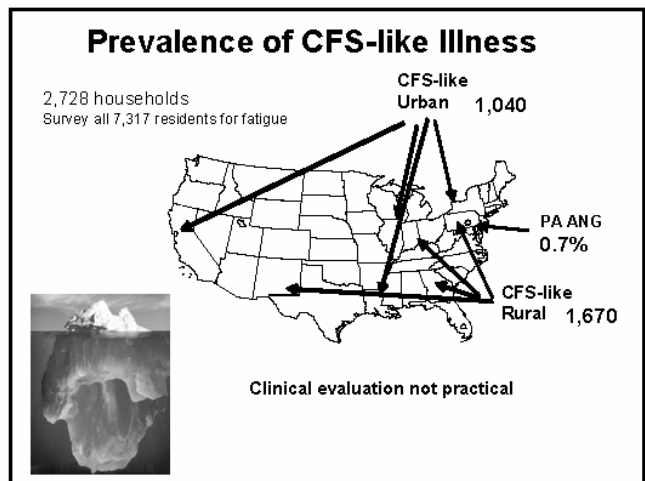
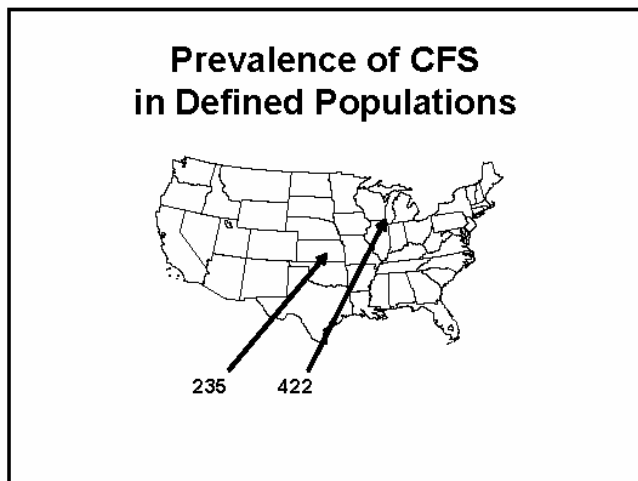
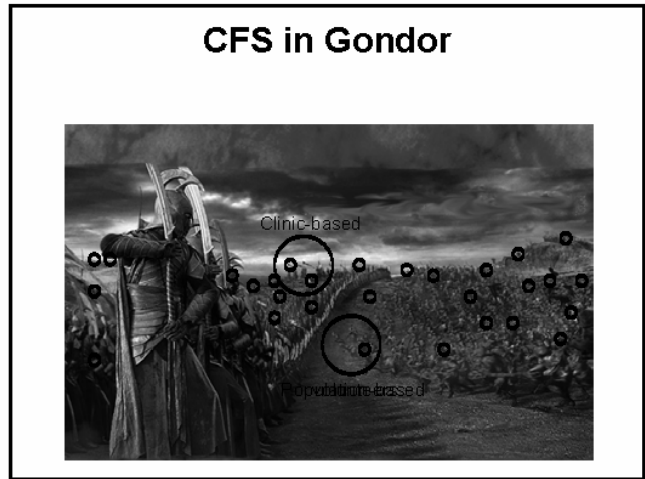
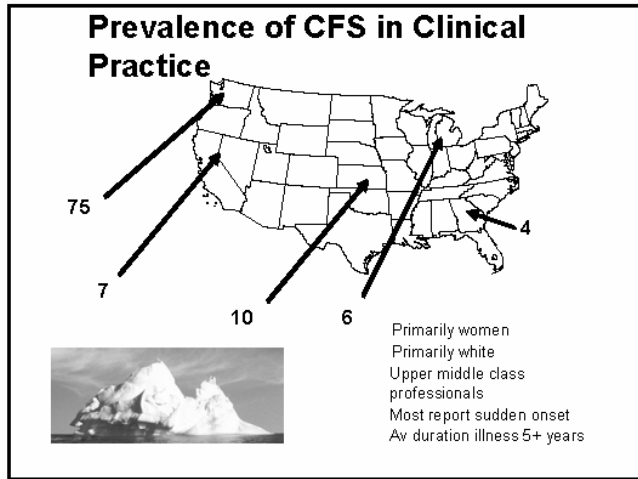
1994 CFS Case Definition

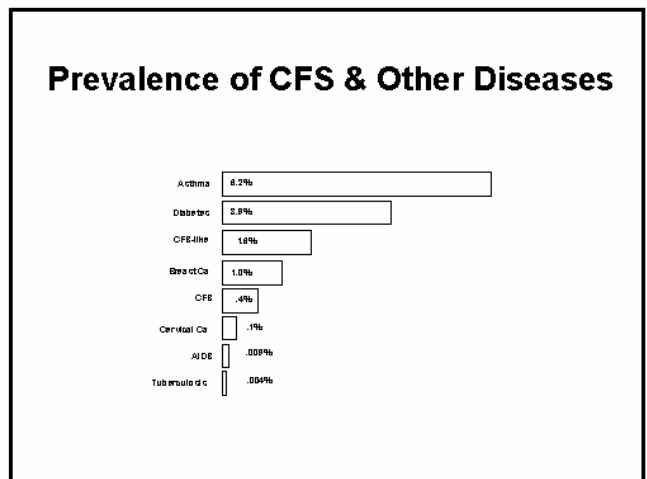
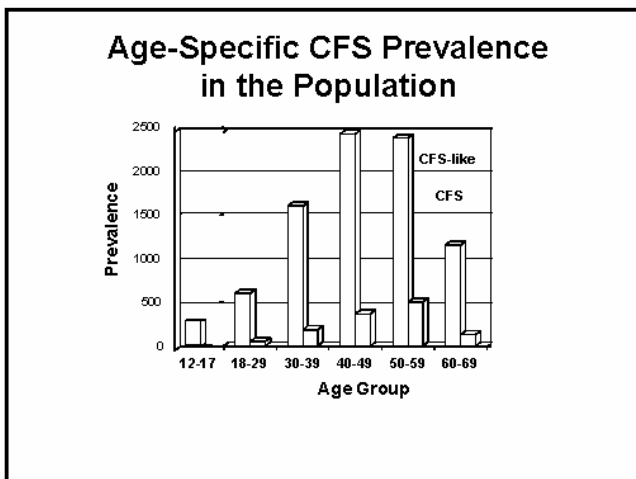
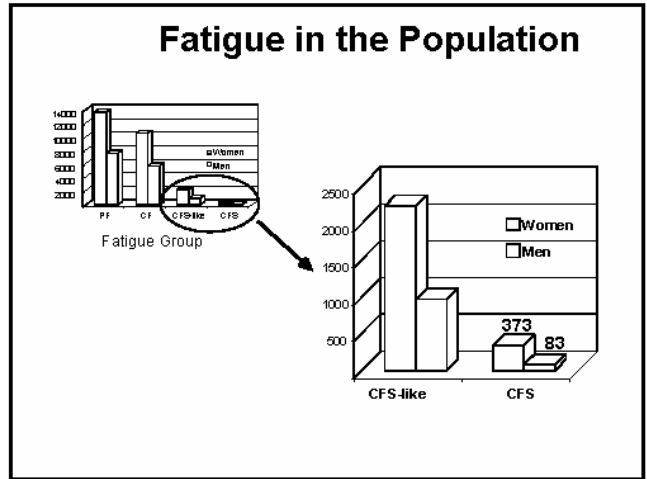
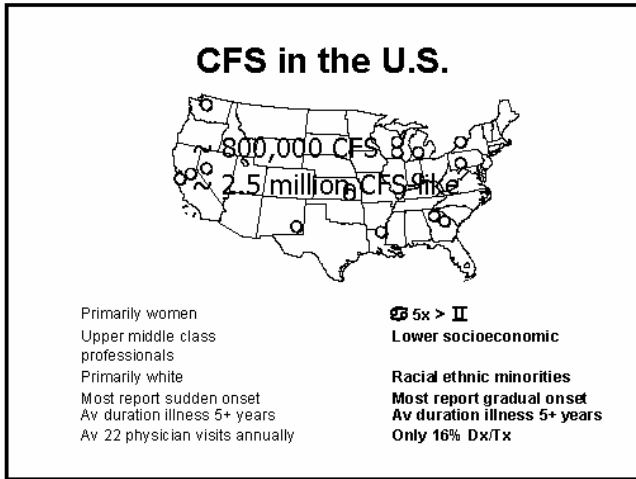
FATIGUE
 Persistent/relapsing > 6 Mo.
 Not alleviated by rest
 Substantial reduction in activities

No explanatory medical or psychiatric causes

Accompanying Symptoms

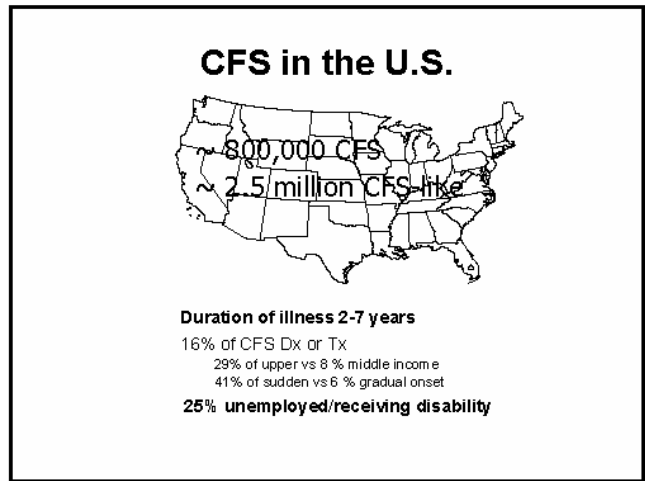
impaired memory/concentration	muscle pain
post exertional fatigue	multi-joint pain
unrefreshing sleep	sore throat
headaches	tender lymph nodes





Impairment and Disability (SF-36)

			NP	CFS	CBD	CCPD	Others	Depressed
Physical activity	Limited a lot performing all physical activities including bathing or dressing due to health	Performs all types of physical activities including the most vigorous without limitations due to health	90	59	46	57	57	72
Social activity	Extreme & frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference due to physical or emotional problems	95	59	71	72	79	57
Role physical	Problems with work or other daily activities due to physical health	No problems with work or other daily activities due to physical health	89	30	34	34	38	44
Role Emotional	Problems with work or other daily activities due to emotional problems	No problems with work or other daily activities due to emotional problems	96	69	64	60	75	40
Bodily pain	Very severe & extremely limiting pain	No pain or limitations due to pain	78	45	63	55	55	59
Mental health	Nervous & depressed all the time	Peaceful, happy, calm all the time	68	74	75	68	78	46
Vitality	Tired or worn out all the time	Peppy and energetic all the time	72	23	44	45	50	40
General health	Personal health poor & likely to get worse	Personal health excellent	85	59	47	45	60	53



CFS - Unanswered Questions



Race/ethnicity
Socioeconomic
Health care utilization
Rural vs. Urban
Economic impact

Risk Factors
Biomarkers

CFS has been studied for more than a decade and there are 3,000 articles in MEDLINE investigating the etiology or markers of CFS.

- Infectious
 - EBV, enteroviruses, HTLV, other viruses
 - Bacteria, rickettsia, novel agents
- Immune function
 - Immune system characterization
 - cell types, cytokines
 - Functional analysis
 - transformation, NK activity
- Neuroendocrine
 - HPA axis
 - Neuroendocrine/immune interaction
- Environmental

CFS has been studied for more than a decade and there are 3,000 articles in MEDLINE investigating the etiology or markers of CFS.



Why haven't we identified a consistent association?

- Problems with case definition
- Studies have been clinic-based
- Only prevalent cases studied
- CFS not amenable to classic case control design

CFS has been studied for more than a decade and there are 3,000 articles in MEDLINE investigating the etiology or markers of CFS.



Why haven't we identified a consistent association?

- Problems with case definition

Problems with Case Definition

FATIGUE

Persistent/relapsing > 6 Mo.

Not alleviated by rest

Substantial reduction in activities

No explanatory medical or psychiatric causes

Accompanying Symptoms

impaired memory/concentration

muscle pain

post exertional fatigue

multi-joint pain

unrefreshing sleep

sore throat

headaches

tender lymph nodes

Limitations of the CFS Case Definition

Developed by consensus not empirically

Based on clinical experience not population-based

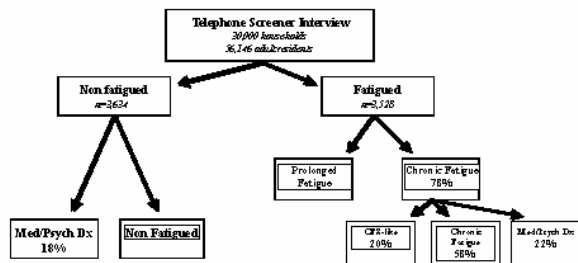
Defined by symptoms and disability

Focuses on Fatigue

Sensitivity/specificity not defined

Specific pathophysiologic process associated with CFS not identified

Empiric Case Definition Population Data Is the Consensus Construct Correct?



Wichita - Symptoms Lasting > 6 Months

• Unrefreshing sleep	62%	• Severe headaches	34%
• Go sleep or wake up	61%	• Numbness/tingling	32%
• Muscle aches/pain	50%	• Shortness of breath	32%
• Joint Pain	49%	• Stomach/abdominal pain	24%
• Sinus/nasal problems	47%	• Diarrhea	16%
• Depression	44%	• Nausea	14%
• Forgetfulness	44%	• Tender lymph nodes	11%
• General weakness	43%	• Chills	11%
• Difficulty thinking	43%	• Sore throat	7%
• Fatigue post exertion	43%	• Fever	6%
• Photophobia	36%		

• 4 CFS Symptoms 13%


Wichita - Factor Analysis

- Dichotomous factor analysis
 - Symptoms coded as 0 or 1
- Exploratory phase (n=718)
 - To estimate number of factors and factor structure
- Confirmatory phase (n=673)
 - To test exploratory model

Wichita - Three-factor Model

	Musculoskeletal	
Muscle aches or pain	89	◆
Joint pain	88	◆
Unusual fatigue post-exertion	48	◆
General weakness	40	
Shortness of breath	31	◆
Sore throat	72	◆
Tender lymph nodes	70	◆
Nausea	61	
Fever	57	
Diarrhea	55	
Stomach or abdominal pain	55	
Chills	41	
Sinus or nasal problems	34	◆
Difficulty thinking or concentrating	80	◆
Forgetfulness or memory problems	75	◆
Unrefreshing sleep	45	◆
Depression	50	
Problems go to sleep or wake up	47	
<i>Factor correlations</i>	<i>0.55, 0.27, 0.33</i>	

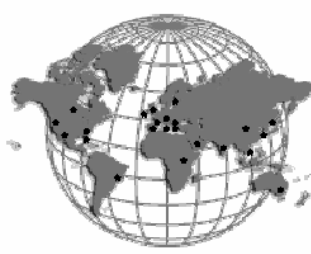
Empiric Case Definition Population Data Is the Consensus Construct Correct?



22 Countries
50 Sites
37,724 chronic fatigue patients

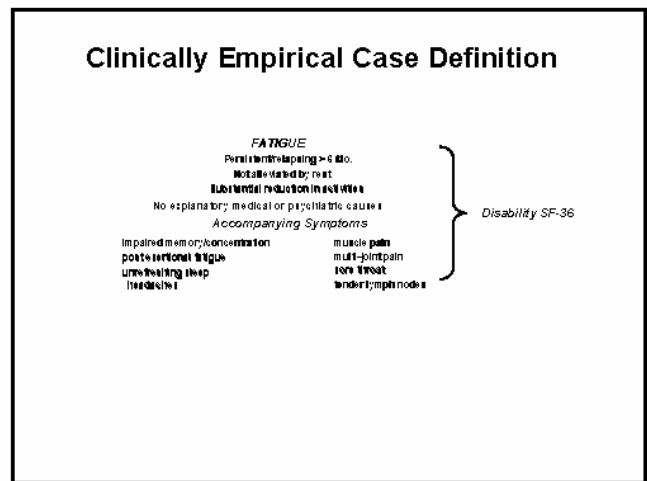
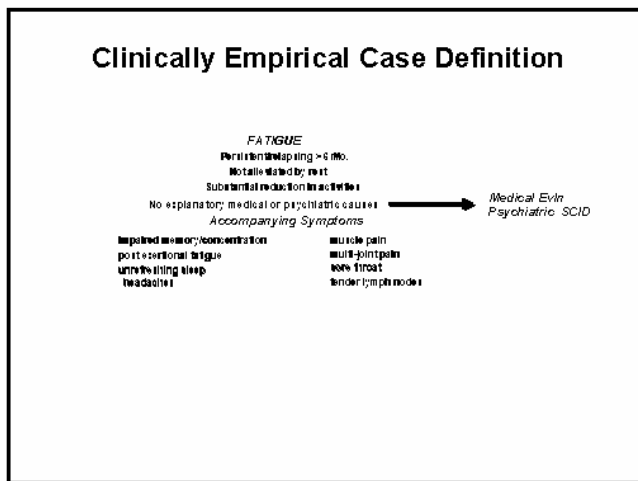
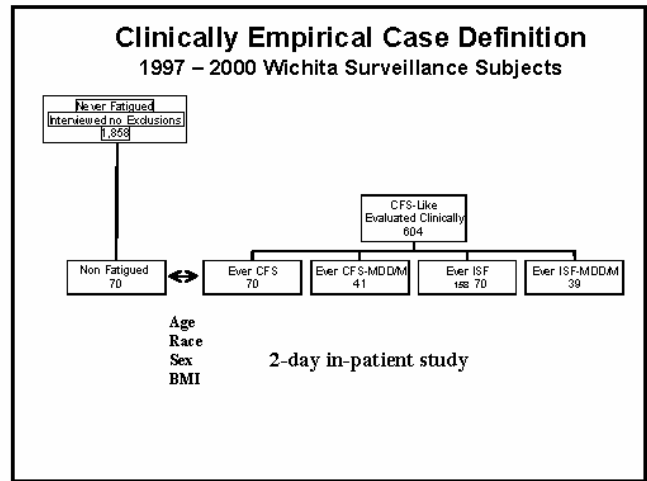
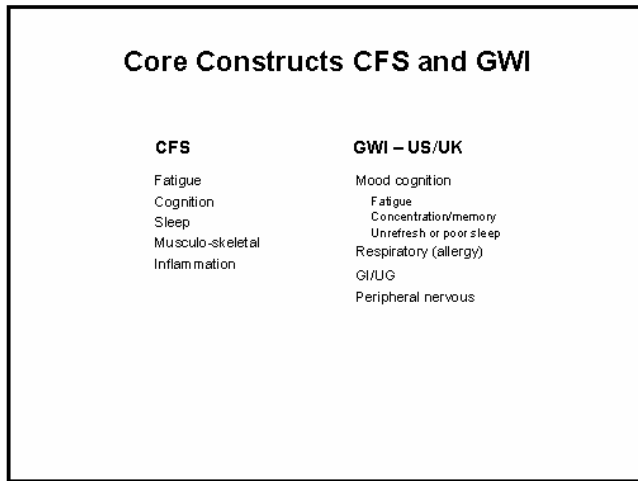
15,749 Community
 19,472 Primary
 2,503 Referral

International Study - Factor Analysis The Construct



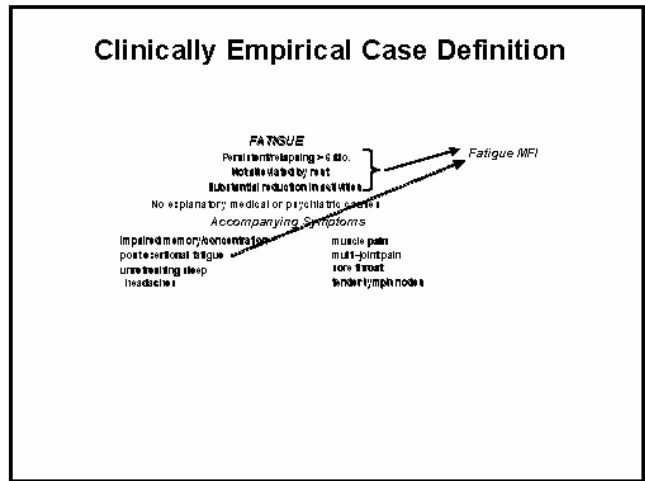
Key Elements
 Mood
 Musculoskeletal
 Inflammation-Infection
 Cognition
 Sleep

Consistent across cultures
Tertiary care unstable



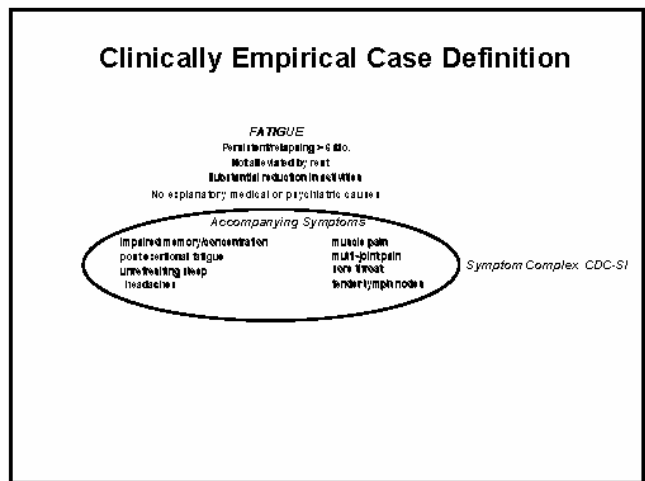
Function/Well Being SF-36

Physical function	Limited a lot performing all physical activities including bathing or dressing due to health	Performs all types of physical activities including the most vigorous without limitations due to health
Social function	Extreme & frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role physical	Problems with work or other daily activities due to physical health	No problems with work or other daily activities due to physical health
Role Emotional	Problems with work or other daily activities due to emotional problems	No problems with work or other daily activities due to emotional problems
Bodily pain	Very severe extremely limiting pain	No pain or limitations due to pain
Mental health	Nervous & depressed all the time	Peaceful, happy, calm all the time
Vitality	Tired or worn out all the time	Pep and energy all the time
General health	Personal health poor & likely to get worse	Personal health excellent



Fatigue Characteristics MFI

General fatigue	I feel fresh	I feel tired
Physical fatigue	Physically I feel able to do a lot	Physically I feel only able to do a little
Mental fatigue	It takes little effort to concentrate	It takes a lot of effort to concentrate
Reduced motivation	I feel I can do anything	I don't feel like doing anything
Reduced activity	I think I do a lot in a day	I think I do very little in a day



Symptom Characteristics CDC Symptom Inventory

- Case Definition
 - Post-exertional malaise
 - Unrefreshing sleep
 - Impaired memory/concentration
 - Muscle pain
 - Multi-joint pain
 - Headaches
 - Sore throat
 - Tender cervical/axillary nodes
- Other symptoms
 - Feverishness
 - Diarrhea
 - Chills
 - Nausea
 - Stomach/abdominal pain
 - Sinus/nasal problems
 - Shortness of breath
 - Sensitivity to light
 - Depression

CDC Symptom Inventory

- Frequency
 - 1 = rarely
 - 2 = Some of the time
 - 3 = Most of the time
 - 4 = All of the time

*

- Intensity
 - 1 = Mild
 - 2.5 = Moderate
 - 4 = Severe

Clinically Empirical Case Definition

SF-36	Physical Function ≤ 70 or Social Function ≤ 75 or Role physical ≤ 50 or Role Emotional ≤ 67 and	
MFI	General fatigue ≥ 13 or Reduced activity ≥ 10 and	
CDC SI	Post-exertional malaise Unrefreshing sleep Impaired memory/concentration Muscle pain Multi-joint pain Headaches Sore throat Tender cervical/axillary nodes	} > 3 Symptoms and Score > 24

Comparison of Standard 1994 and Clinically Empirical Definitions

Standard 1994 Definition	Empiric Definition			
	CFS	ISF	NF	
CFS	10 (63%)	6 (38%)	0	16
ISF	32 (42%)	38 (50%)	6 (8%)	76
Not Fatigued	0	13 (18%)	58 (82%)	71
	42	57	64	

Correlations of disability, fatigue, and symptoms with classification

	CFS	ISF	NF
<i>Physical function</i>	53	77	90
<i>Social function</i>	50	74	95
<i>Role physical</i>	18	61	89
<i>Role Emotional</i>	56	76	96
Bodily pain	42	60	78
Mental health	66	75	87
General health	51	70	85
Vitality	19	37	72
<i>General fatigue</i>	18	15	8
<i>Reduced activity</i>	15	11	6
Physical fatigue	14	11	7
Mental fatigue	14	10	7
Reduced motivation	12	10	6
Symptom Inventory	47	18	6

Other Parameters to Evaluate in Context of Clinically Empirical Case Definition

- Polysomnography
- Cognitive Function
- Autonomic Nervous System
- Neuroendocrine
- Immune system
- Psychometrics
- Gene Activity
- Proteomics

CFS has been studied for more than a decade and there are 3,000 articles in MEDLINE investigating the etiology or markers of CFS.

Why haven't we identified a consistent association?

- Studies have been clinic-based
- Only prevalent cases studied



CFS Not Amenable to Classic Case-Control Design

CFS is a Complex Illness

- Illness represents alterations in complex systems of homeostasis
- Not a result of a single mutation or single environmental factor
- Arise from a combined action of many genes, environmental factors and risk-conferring behavior
- Understanding complex illness may elucidate the common pathways of other complex diseases



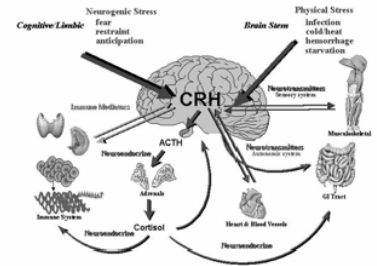
CFS is a Complex Illness

The pathophysiology of CFS appears to involve afferent and efferent pathways of brain-body communication



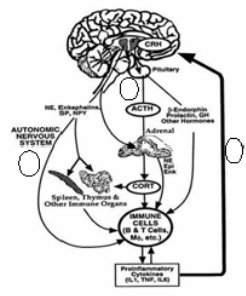
CFS is a Complex Illness

The pathophysiology of CFS appears to involve afferent and efferent pathways of brain-body communication

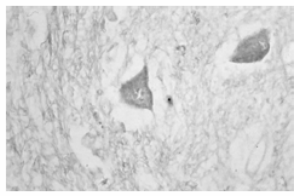


CFS, what to sample?

- No identified lesion
- What sample representative of CFS disease?

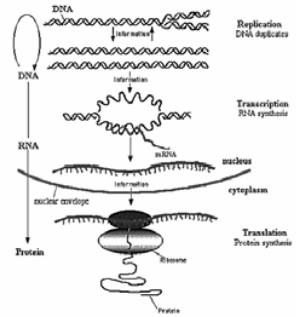


Is Peripheral Blood a Reasonable Sample?

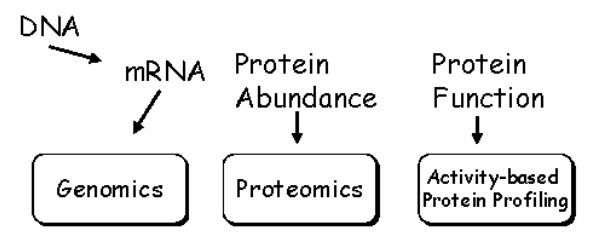


- PBMC reflect immune system
- PBMC reflect endocrine system
- Leukocytes in CNS in normal and disease states
 - Activated T cells - enter/leave
 - NK cells - enter/leave
 - B cells - random traffic
 - Monocytes - assist in maintenance and function of BBB enter/leave CNS

Central Dogma of Molecular Biology



Biomarker Discovery Strategy



Gene Expression Profiling

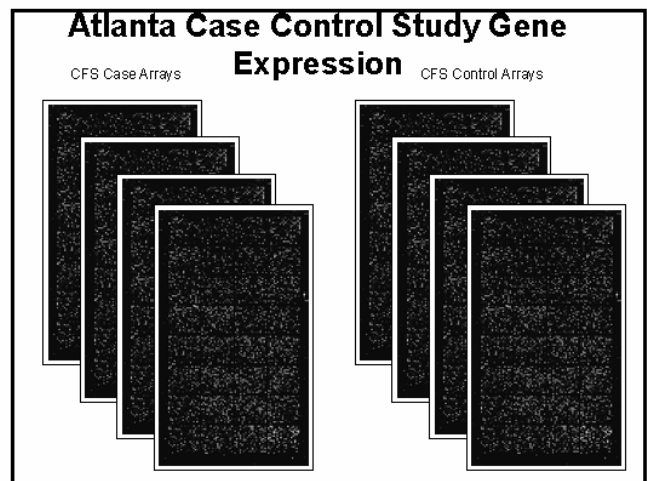
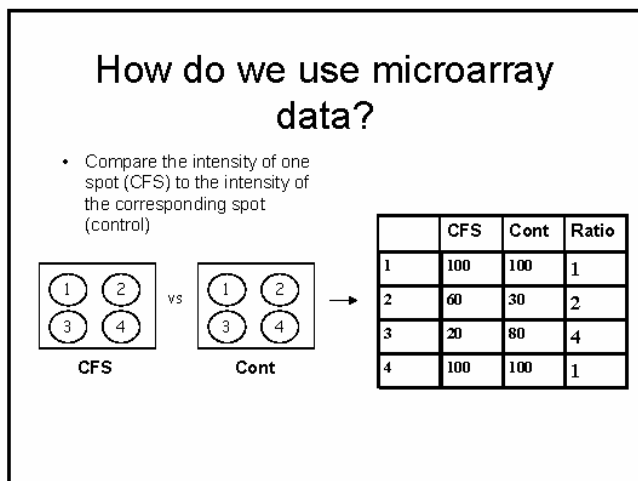
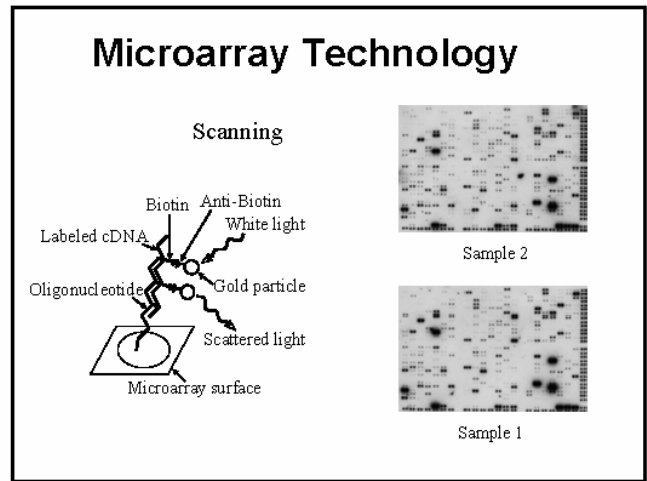
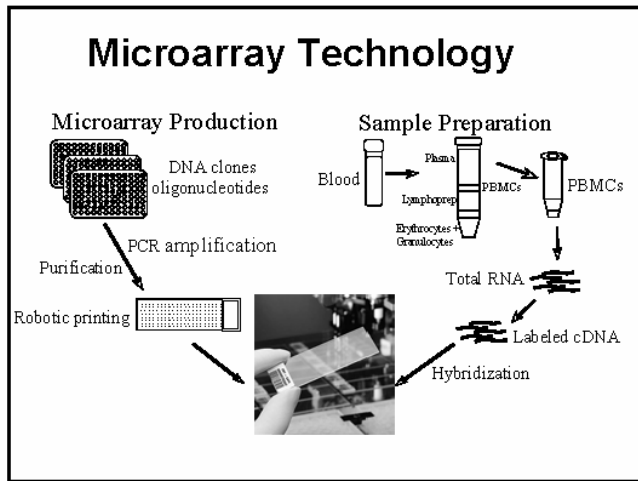
- An attempt to measure expression levels of all genes in a cell and to correlate the pattern with disease phenotype

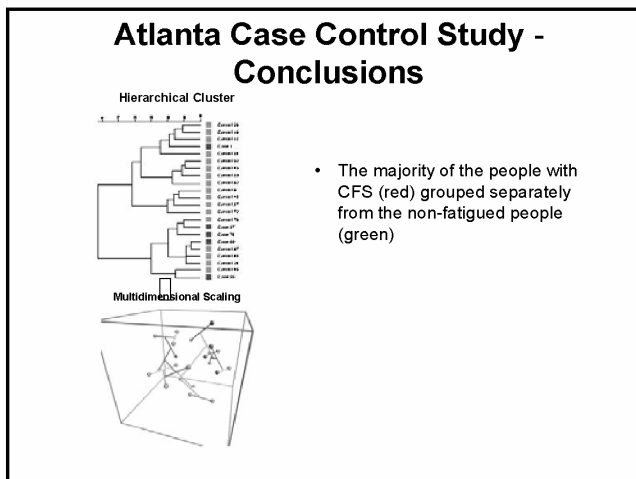
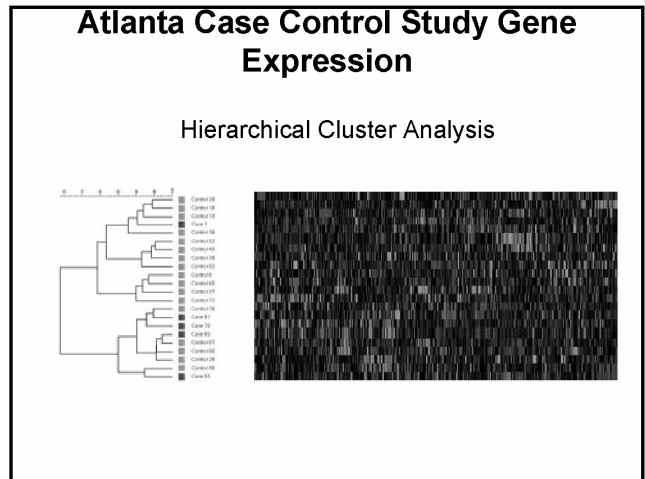
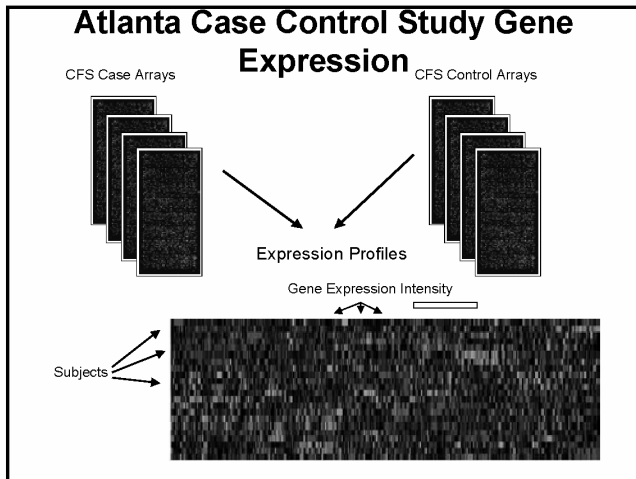


Gene Expression Profiling

- An attempt to measure expression levels of all genes in a cell and to correlate the pattern with disease phenotype







To Empirically Subtype CFS

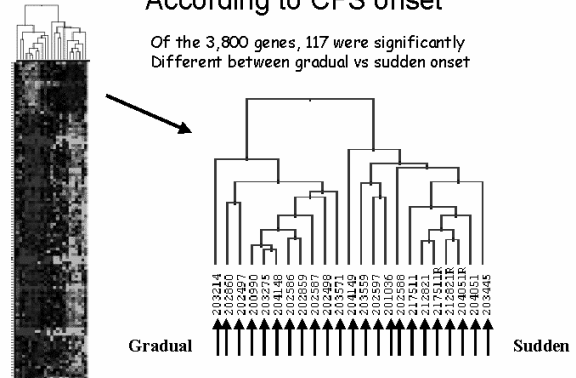
- 23 women with CFS from Wichita
- Measure expression of 3,800 genes
- Question:
 - Could gene expression profiles and differentially expressed genes distinguish subtypes of CFS?

Gene Expression to Define CFS ...

- Gene expression profiles compared by clinical characteristics
 - Gradual onset versus sudden onset
 - ≤50 years of age versus >50 years of age
 - ≤10 years of illness vs. >10 years of illness
 - 4 or 5 symptoms vs. ≥6 symptoms
 - Body mass index (normal, overweight, obese)
 - Symptom severity group

Hierarchical cluster analysis on genes According to CFS onset

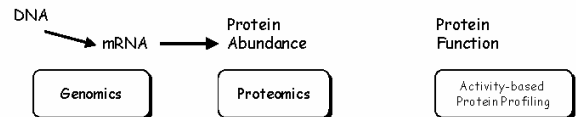
Of the 3,800 genes, 117 were significantly Different between gradual vs sudden onset



CFS Subtyping - Conclusions

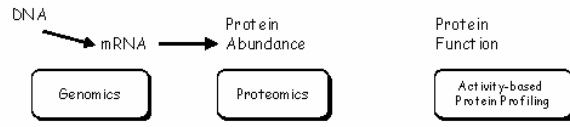
- First "molecular" evidence of a difference between people whose CFS occurred suddenly & those with gradual illness onset
- Different profiles imply different pathophysiology
- Several immune, endocrine and metabolic genes and pathways involved
- Differentially expressed genes in RNA processing and metabolic pathways account for most of the (significant) differences between CFS and controls

Biomarker Discovery Strategy



- Gene expression of PBMC tells us how the body is responding to the illness from the perspective of the PBMC

Biomarker Discovery Strategy

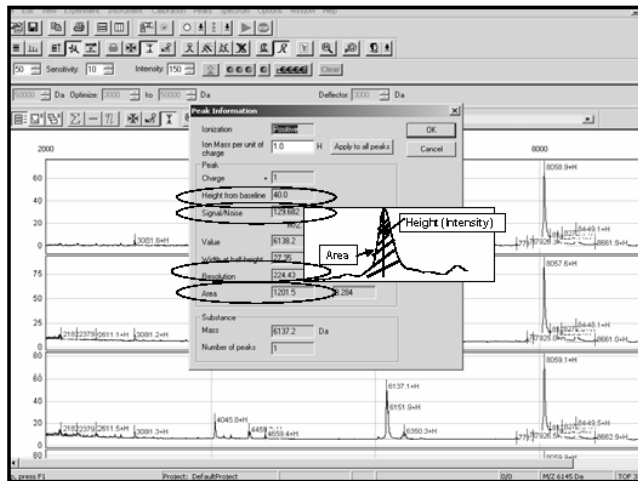
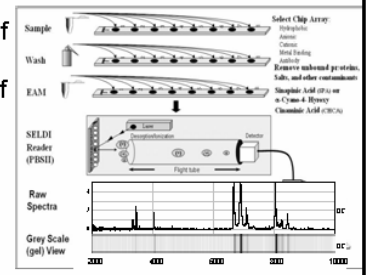


- Gene expression of PBMC tells us how the body is responding to the illness from the perspective of the PBMC
- Protein profiling (proteomics) of the serum will tell us about any process going on in the body
 - Serum is ideal for biomarker discovery as it samples that entire body and contains protein spillover from most bodily processes

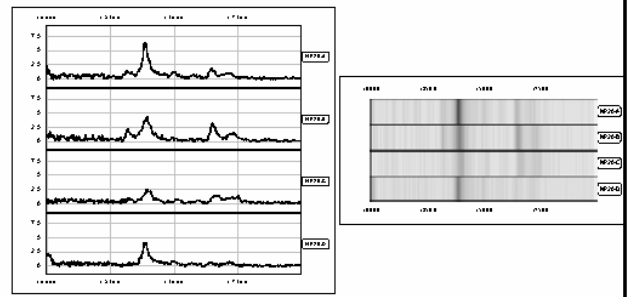
Proteomics

- Mass spectrometry of serum proteins to identify biomarkers of disease and to characterize the pathophysiology of disease

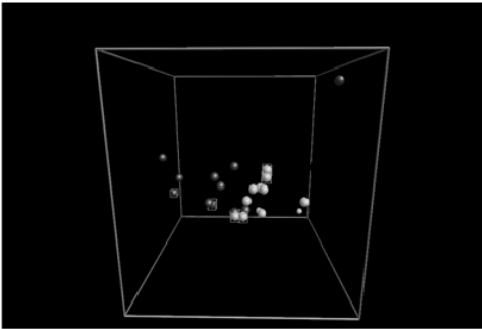
SELDI-TOF



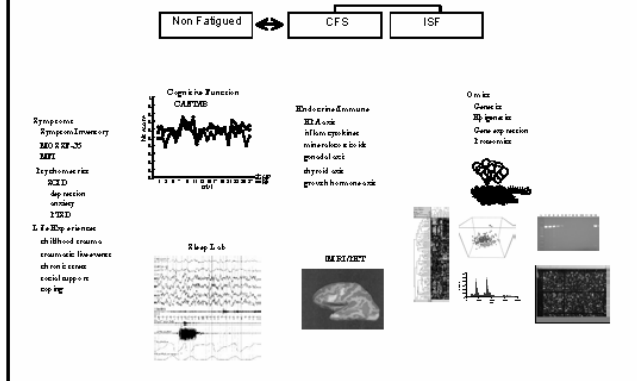
SELDI-TOF Output



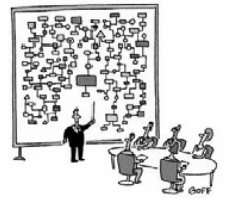
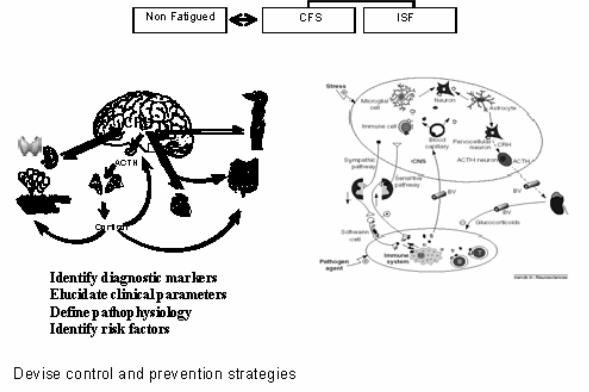
Denver Modeling Study SELDI-TOF Principal Components Analysis



Putting It All Together



Putting It All Together



"And that's why we need a computer."

