Presentation 3 – Nancy Klimas

Immune abnormalities associated with CFS in the general population

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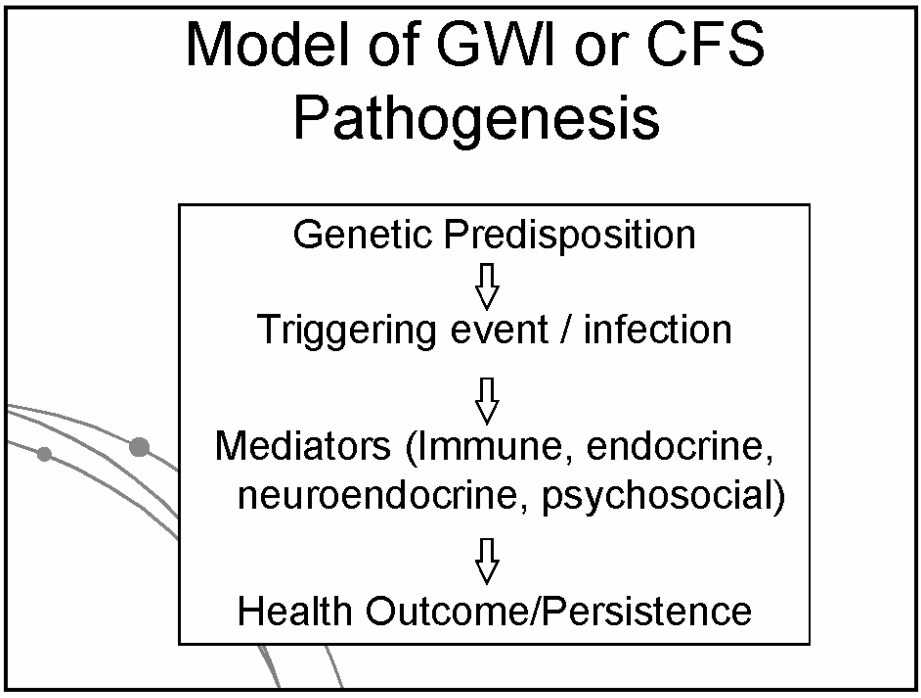
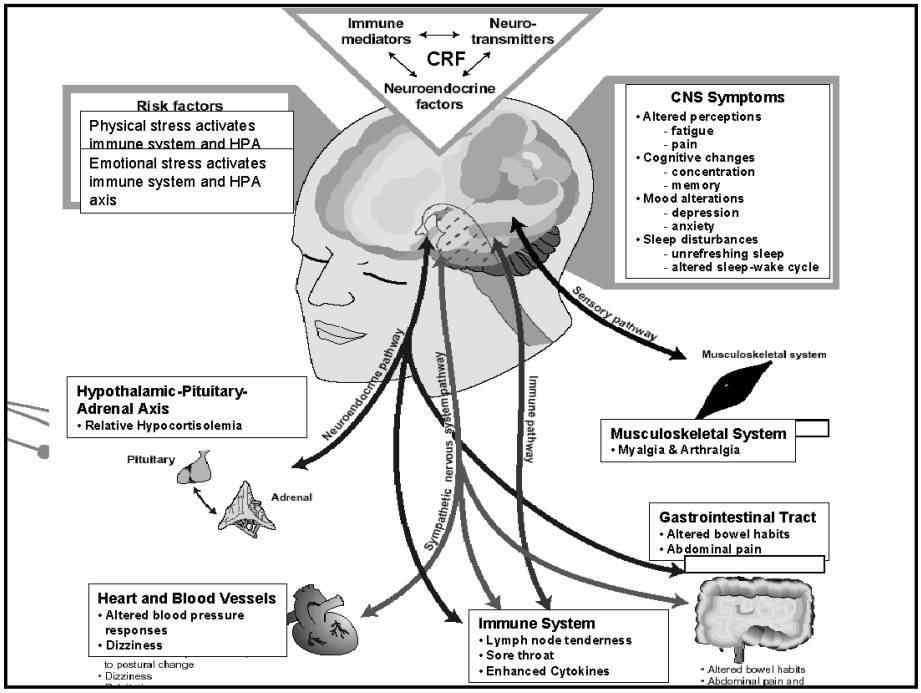
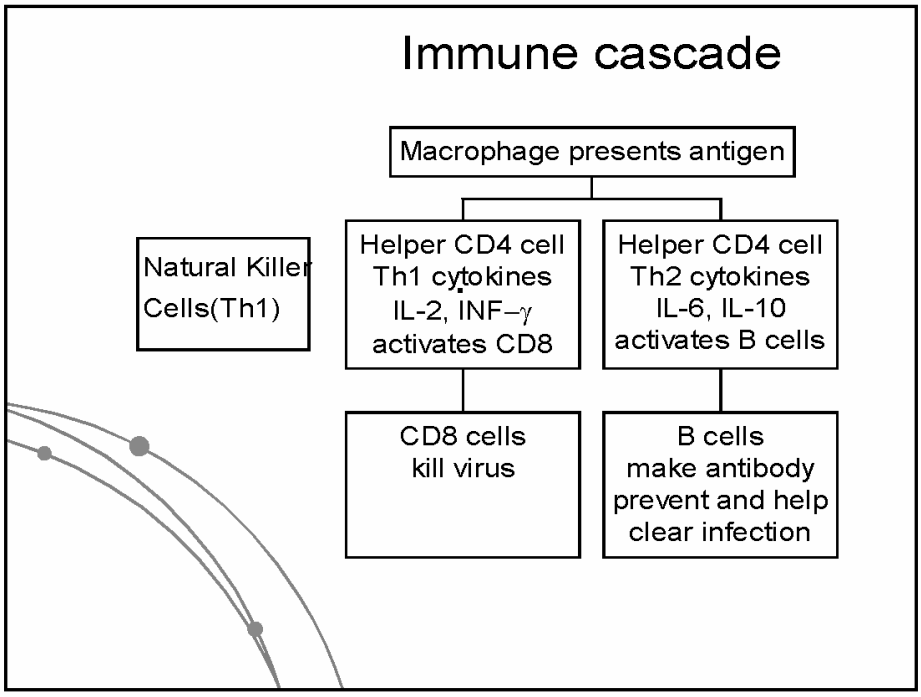
GWI and CFS : Comparisons

- Both defined by symptoms which overlap
- Significant overlap in research findings
- Study of GW veterans showed a 16 fold increase risk of CFS, but no other increased risk over controls
- Issues surrounding the study of a multisymptom illness with a multisystem pathogenesis are the same

Gulf War Illness	Chronic Fatigue Syndrome***
Fatigue	Disabling fatigue
Depression	Exercise induced relapse
Arthralgia	Arthralgia
Myalgia	Myalgia
Sleep disturbance	Non restorative sleep
Cognitive dysfunction	Cognitive dysfunction
Headache	Headache
Diarrhea, intermittent	Sore throat
Wheezing, Cough, Chest pain, Shortness of breath*	Tender lymph nodes
Weight loss, low grade fever**	

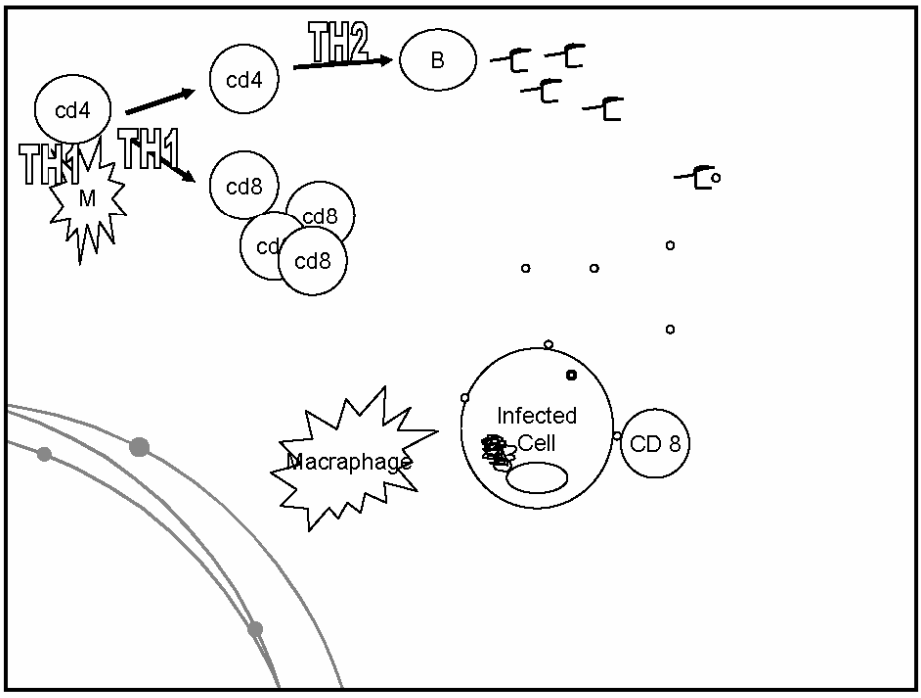


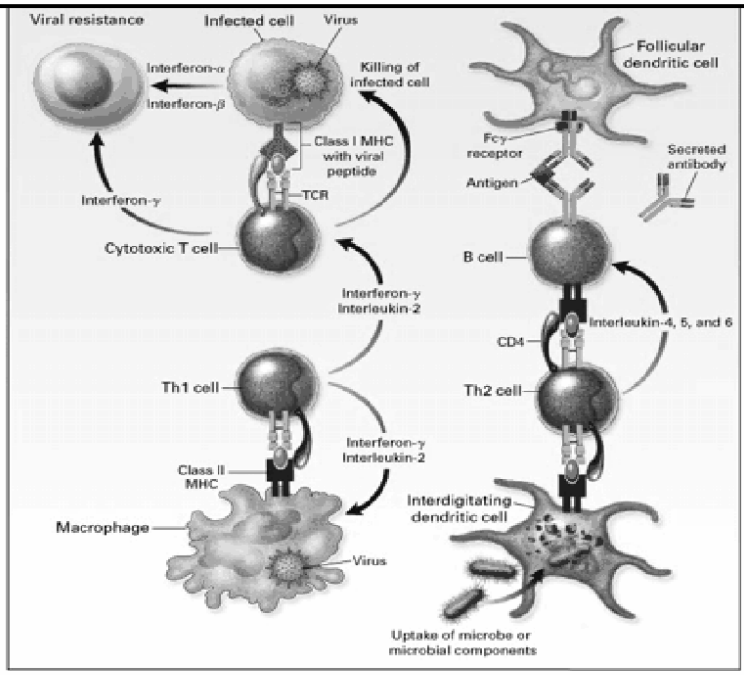

Immune mediators
Neuro-transmitters
CRF
Neuroendocrine factors
Risk factors
Physical stress activates immune system and HPA
Emotional stress activates immune system and HPA axis
CNS Symptoms
• Altered perceptions
- fatigue
- pain
• Cognitive changes
- concentration
- memory
• Mood alterations
- depression
- anxiety
• Sleep disturbances
- unrefreshing sleep
- altered sleep-wake cycle
Sensory pathway
Musculoskeletal system
Musculoskeletal System
• Myalgia & Arthralgia
Hypothalamic-Pituitary-Adrenal Axis
• Relative Hypocortisolemia
Neuroendocrine pathway
Sympathetic nervous system pathway
Immune pathway
Pituitary
Adrenal
Gastrointestinal Tract
• Altered bowel habits
• Abdominal pain
Heart and Blood Vessels
• Altered blood pressure responses
• Dizziness
to postural change
• Dizziness
Immune System
• Lymph node tenderness
• Sore throat
• Enhanced Cytokines
• Altered bowel habits
• Abdominal pain and


Immune cascade
Macrophage presents antigen
Natural Killer Cells(Th1)
Helper CD4 cell Th1 cytokines IL-2, INF–γ activates CD8
Helper CD4 cell Th2 cytokines IL-6, IL-10 activates B cells
CD8 cells kill virus
B cells make antibody prevent and help clear infection

Cytokines Patterns

- Type 1 - promote cell mediated immunity, antiviral responses. INF-g, IL-2, IL-12
- Type 2 - promote antibody production. IL-4, IL-5,IL-10
- Pro-inflammatory - mediate inflammatory responses. TNF-a, IL-1, IL-6



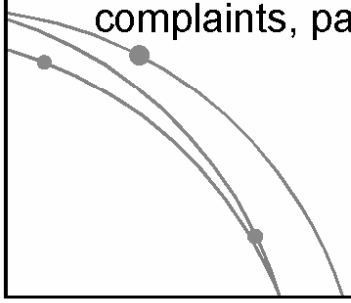


Cytokines and the Immune System

- Lymphocytes and associated cells - function through a messenger system using cytokines.
- Cytokines deliver message from cell to cell, promoting cell growth, enhancing cell functions, turning off cell functions, and promoting cell death (apoptosis).

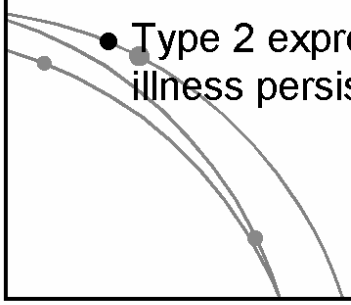
Cytokines in CFS

- Th 2 imbalance
- Proinflammatory cytokine expression
- Activation of inflammatory cascade correlates with severity of cognitive complaints, pain



Cytokine Changes Over Time

- Patterns of cytokine expression change with illness severity
- TNF-a receptor expression increases with flares of illness (Patarca et al, 1996)
- Type 2 expression increasingly evident as illness persists for years

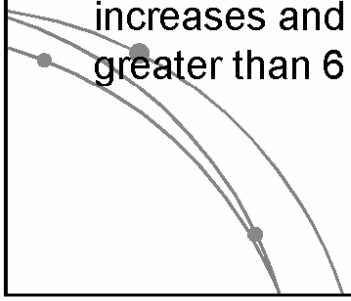


Severity of Illness correlates with pro-inflammatory cytokine levels

- Hurricane Andrew study

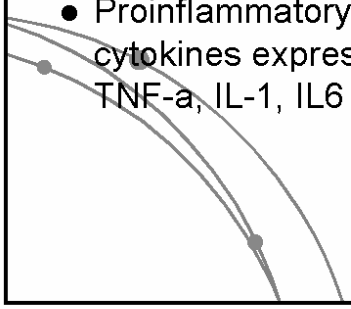
Increase in cognitive difficulties directly correlated with IL1 increase

Post hurricane relapse resulted in cytokine increases and relapse that persisted greater than 6 months



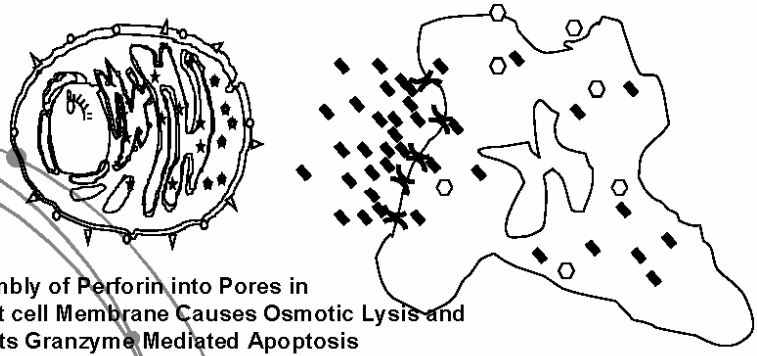
Immune abnormalities in CFS

Immune Activation	Functional defects
• DR, CD26 expression	NK Cell dysfunction
• TH2 cytokine shift	CD8 abnormalities
• Proinflammatory cytokines expression TNF-a, IL-1, IL6	perforins, granzymes ↓
	Macrophage abnormalities
	Antibody production

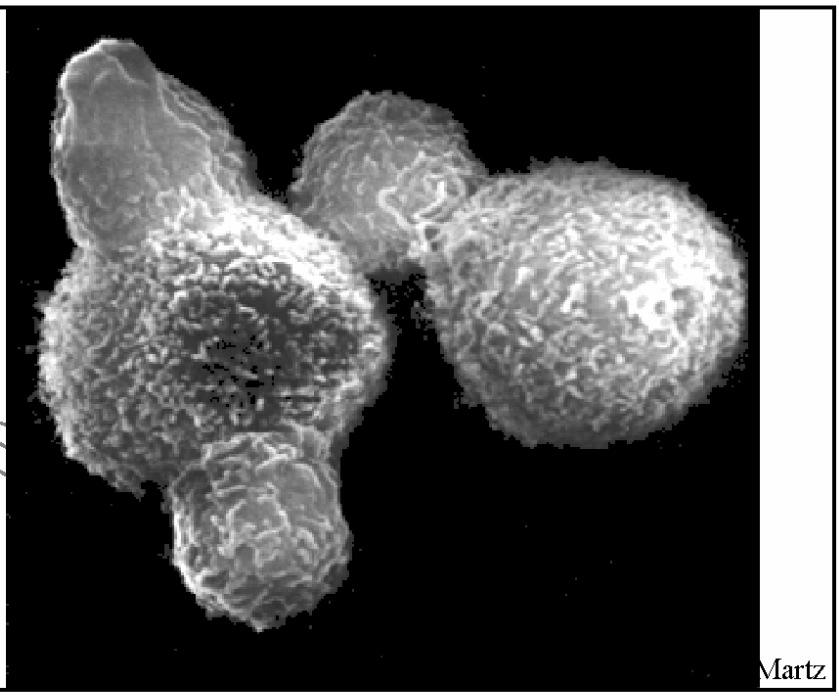


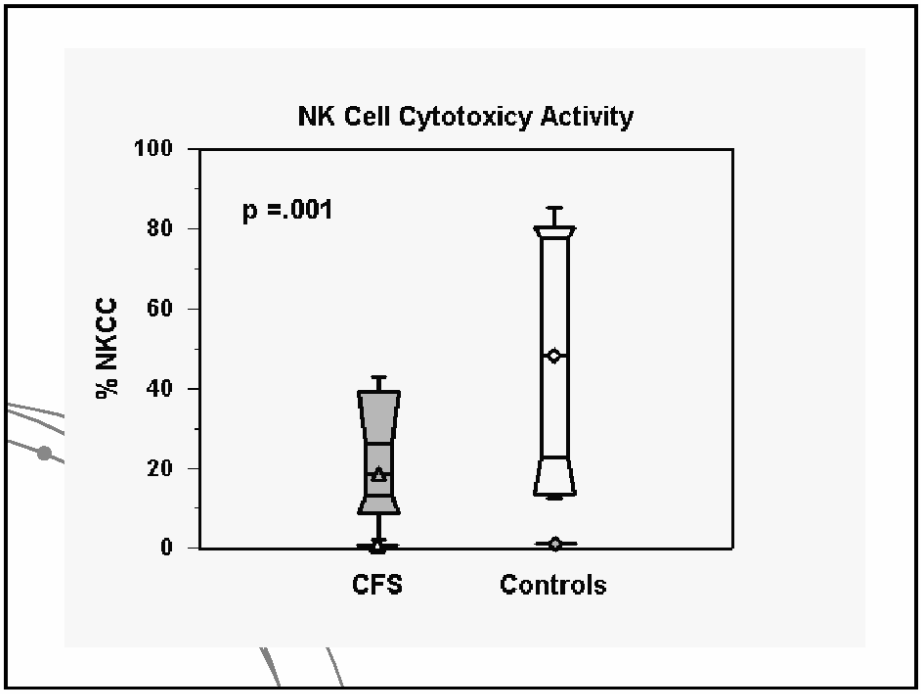
Natural Killer Cell Cytotoxicity

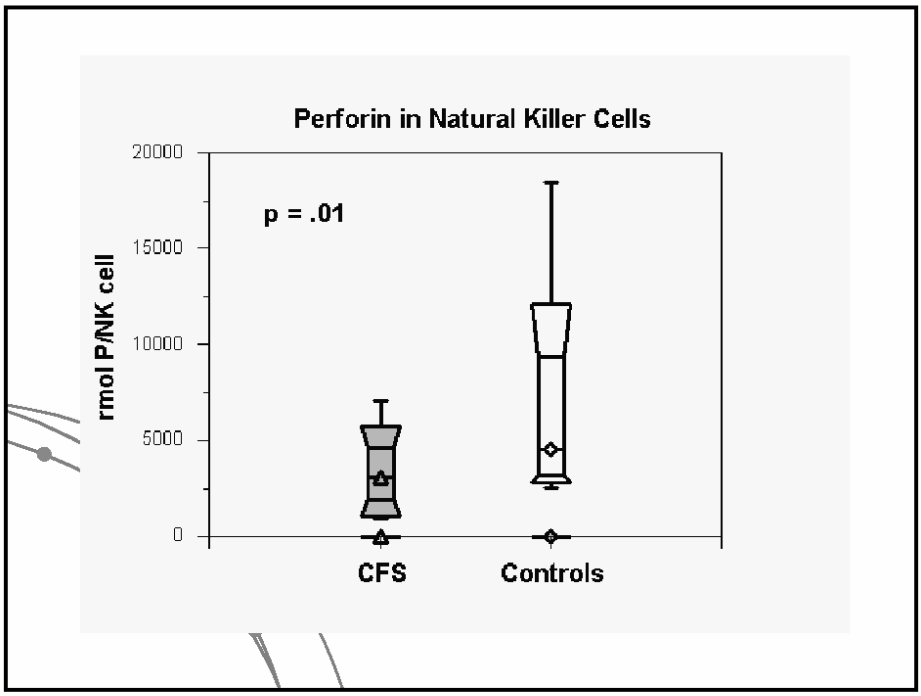
Abnormal Cell Recognition

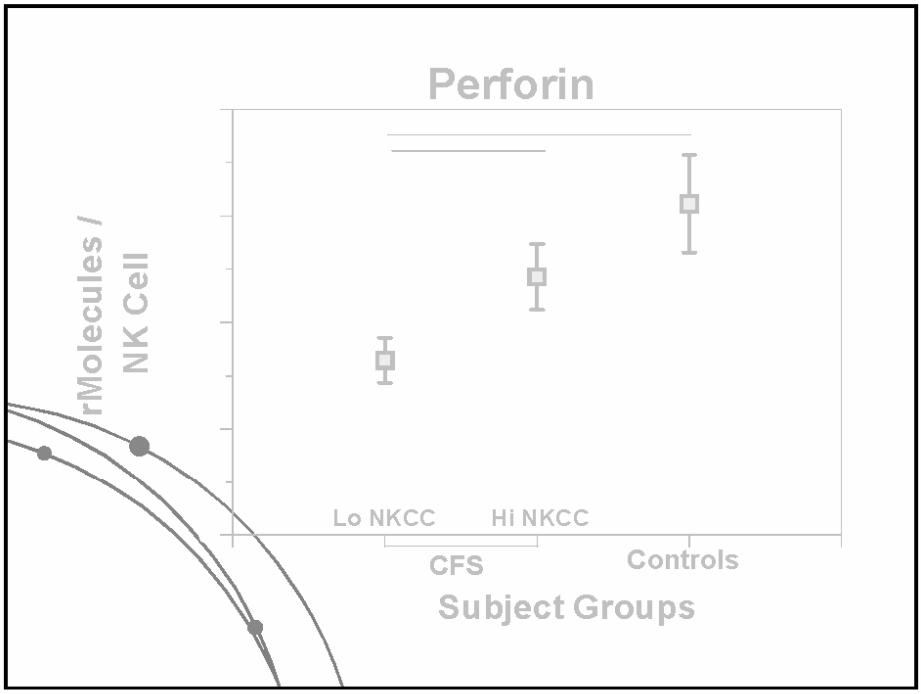


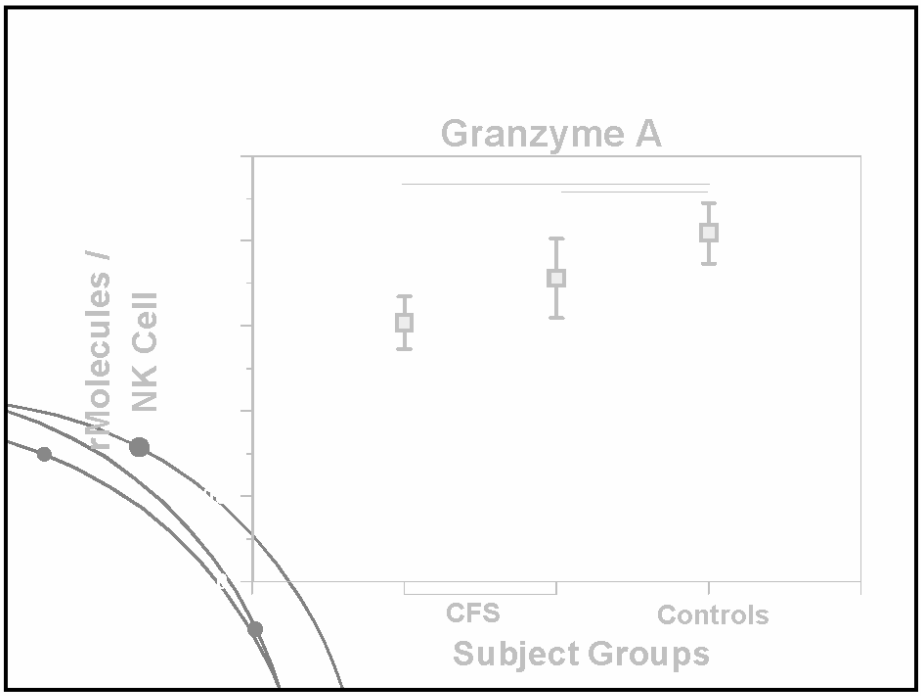
Assembly of Perforin into Pores in
Target cell Membrane Causes Osmotic Lysis and
Permits Granzyme Mediated Apoptosis

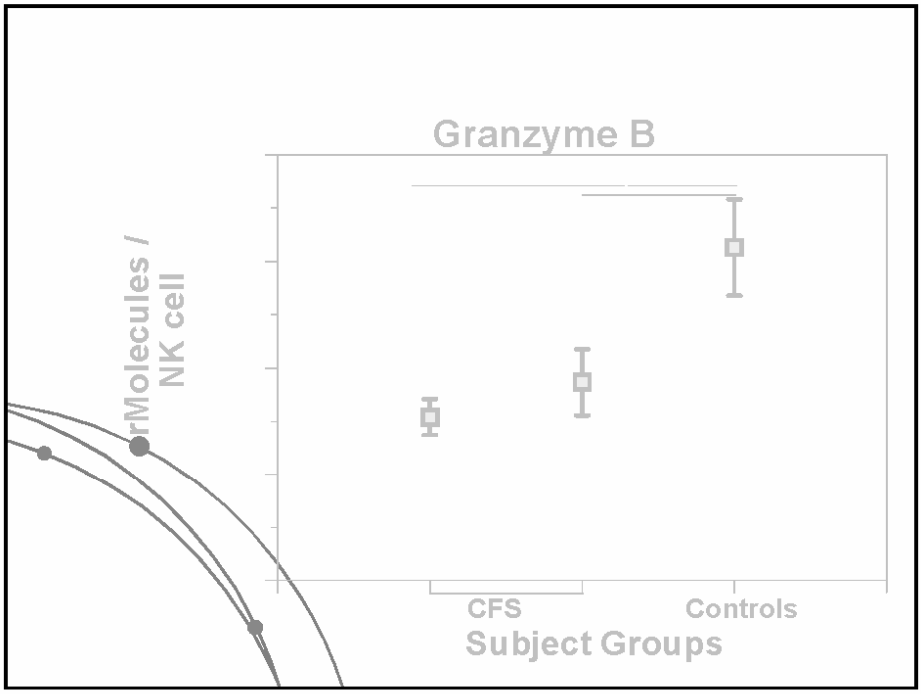


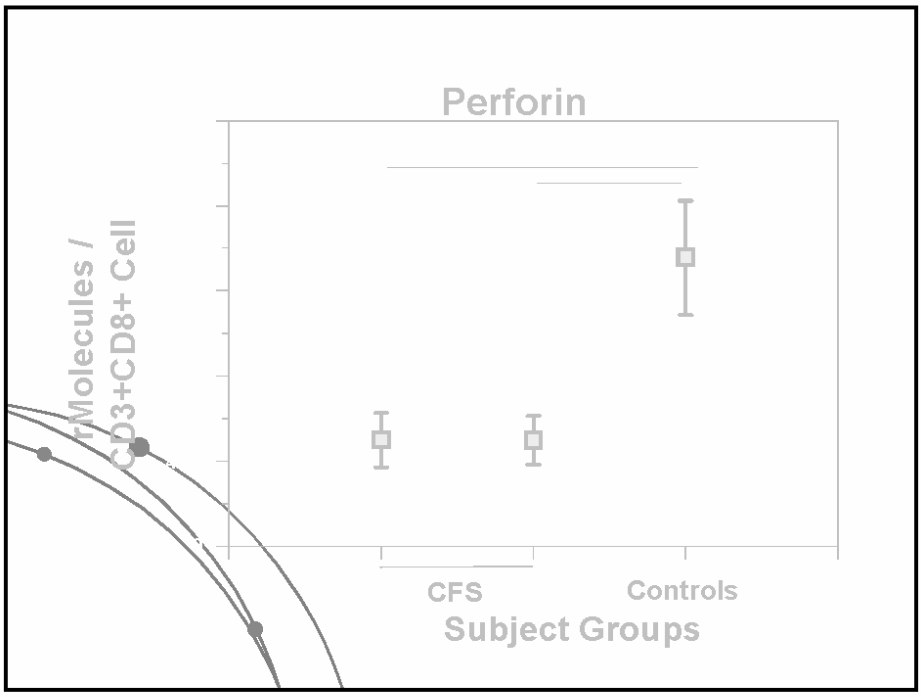

NK Cell Cytotoxicy Activity
p =.001
% NKCC
100
80
60
40
20
0
CFS
Controls

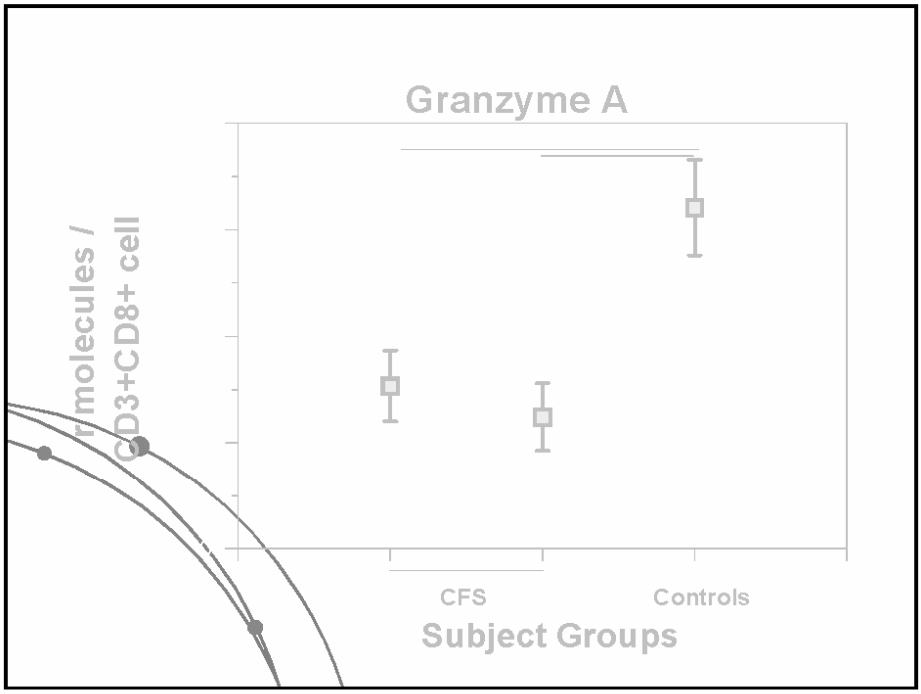

Perforin in Natural Killer Cells
p = .01
rmol P/NK cell
20000
15000
10000
5000
0
CFS
Controls

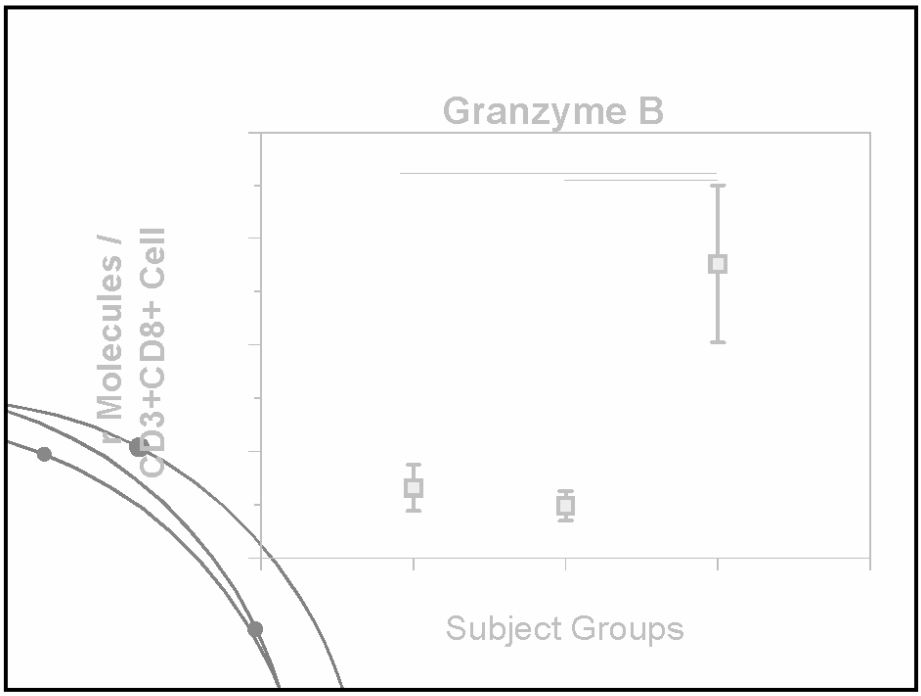

Perforin
rMolecules /
NK Cell
Lo NKCC
Hi NKCC
CFS
Controls
Subject Groups

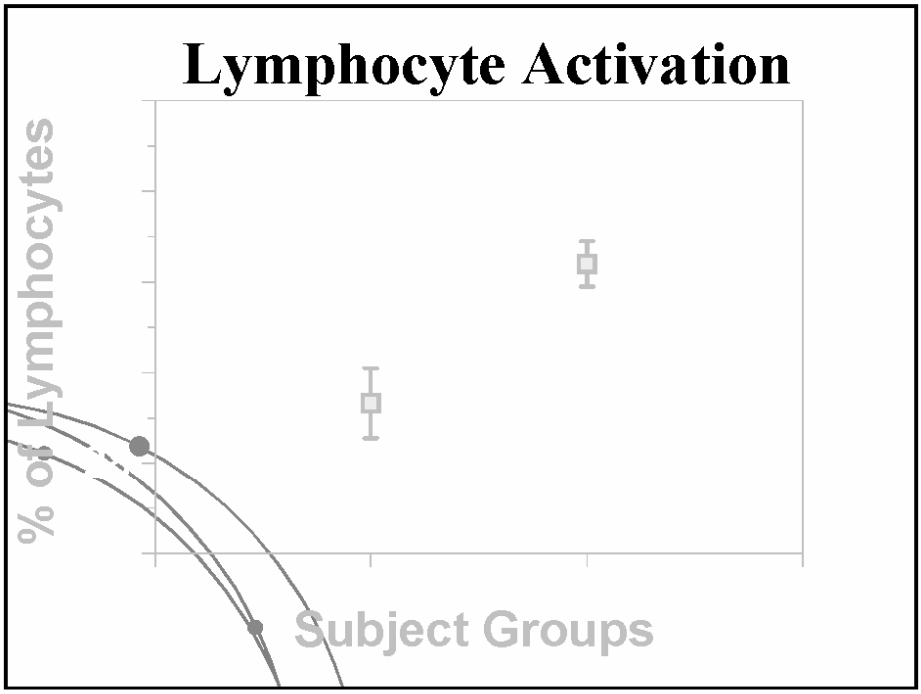

Granzyme A
rMolecules /
NK Cell
CFS
Controls
Subject Groups

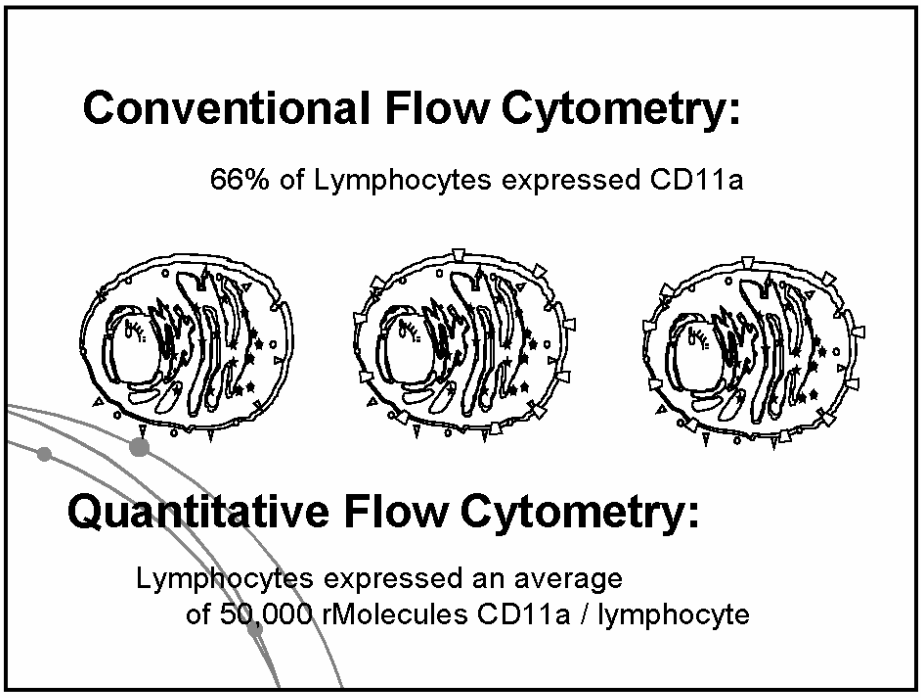

Granzyme B
rMolecules /
NK cell
CFS
Controls
Subject Groups

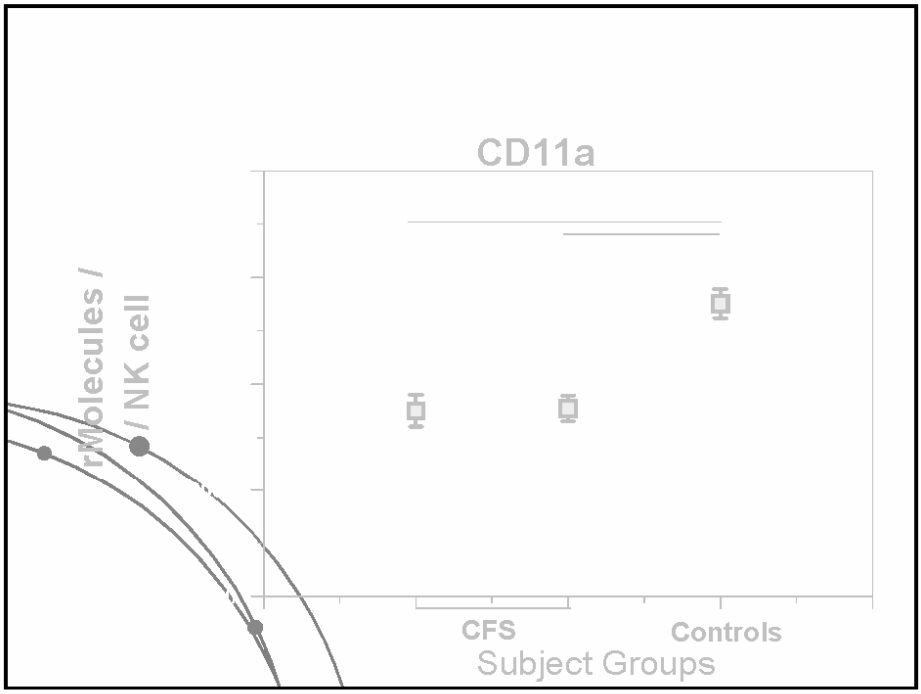

Perforin
rMolecules /
CD3+CD8+ Cell
CFS
Controls
Subject Groups

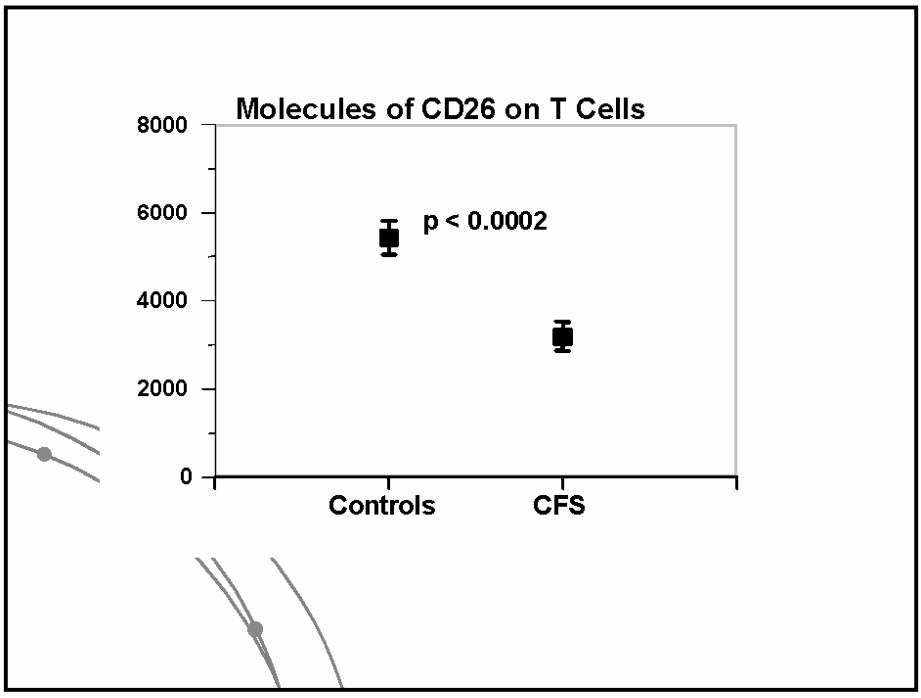

Granzyme A
r molecules /
CD3+CD8+ cell
CFS
Controls
Subject Groups

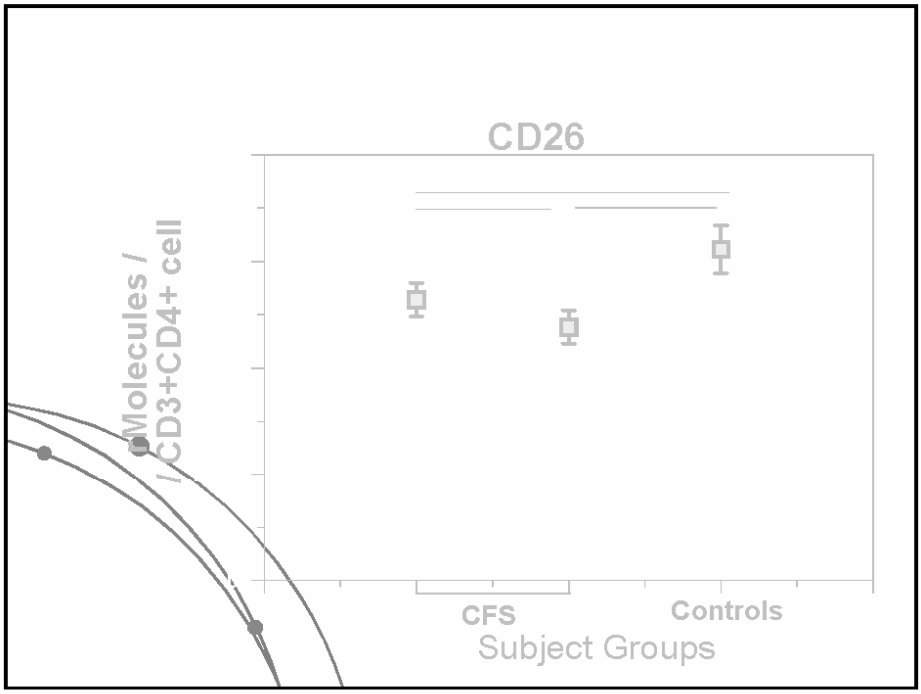

Granzyme B
r Molecules /
CD3+CD8+ Cell
Subject Groups


Lymphocyte Activation
% of Lymphocytes
Subject Groups


Conventional Flow Cytometry:
66% of Lymphocytes expressed CD11a
Quantitative Flow Cytometry:
Lymphocytes expressed an average
of 50,000 rMolecules CD11a / lymphocyte


CD11a
rMolecules /
/ NK cell
CFS
Controls
Subject Groups


Molecules of CD26 on T Cells
8000
6000
4000
2000
0
p < 0.0002
Controls
CFS



Immune abnormalities in CFS

Immune Activation	Functional defects
• DR, CD26 expression • TH2 cytokine shift • Proinflammatory cytokines expression TNF-a, IL-1, IL6	NK Cell dysfunction CD8 abnormalities ↓ perforins, granzymes Macrophage abnormalities Antibody production Cell receptor expression

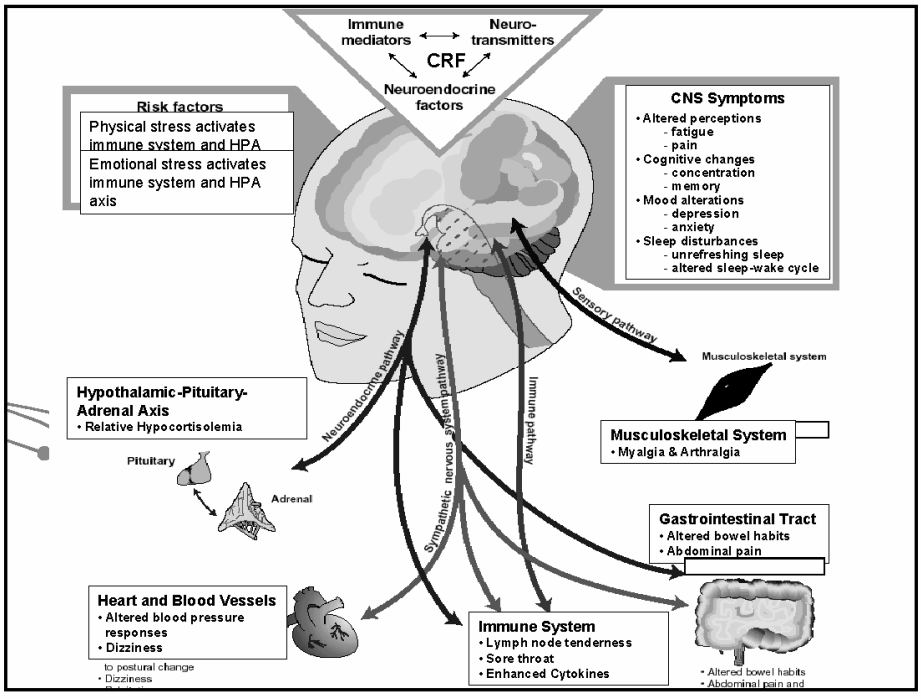
Gulf War Illness

- Immune Activation

- Higher T and B cell numbers
- Reduced NK, T and B cell function in vitro
- Elevations in immune complexes
- Autoantibody titers directed against MBP and striated or smooth muscle
- Elevated titers to EBV, HSV, HHV6

- Cytokine shift, IL10 over expression – increasing INF gamma/IL10 with increasing vaccine exposure
- 2 groups, TH1 or TH2 ; TH2 cytokine shift with pro-inflammatory cytokines TNF-a, correlating with cognitive impairment

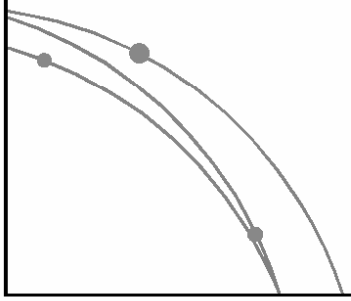
- Voldal A Environ Health Perspect. 2004 Jun;112(8):840-6
- Skowera A, J Clin Immunol. 2004 Jan;24(1):66-73.
- Ferguson and Cassaday Behav Neuro 2002 10(2):93
- Peakman 2004 J Clin Immonol 24(1):60
- Natelson Neuroimmunomodulation 10(2):93



Immune Mediator interactions

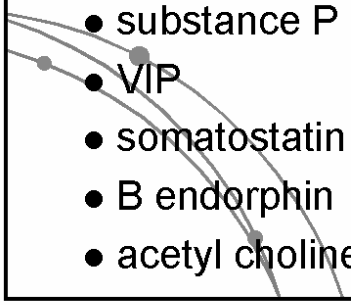
Immune neuropeptide interactions

- Immune - Autonomic
- Immune - HPA
- Immune - Sleep



Neuro immune connections: receptors in WBCs

- epinephrine, norepinephrine
- seritonin
- substance P (neurogenic inflammation)
- VIP
- somatostatin
- B endorphin
- acetyl choline



Endocrine immune interactions

- Cortisol decreases inflammation through down regulation of immune activation, therefore low cortisol in CFS could play a role in chronic immune activation
- GH and thyroid impact on cell metabolism
- Autonomic impact on lymphocyte function
- models: stress, depression

Stress Response and Immune Function

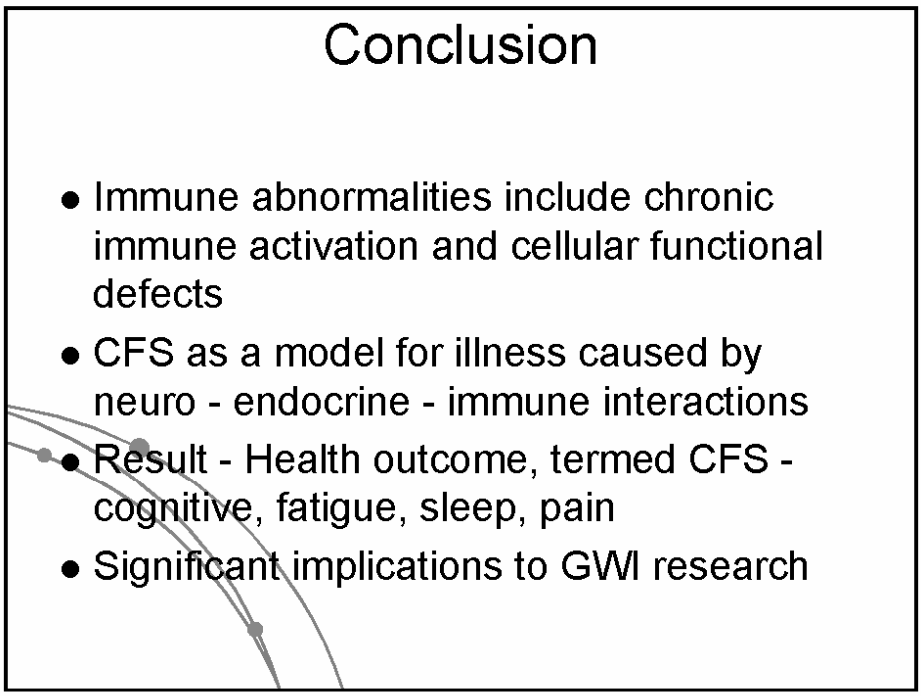
- Short term - "fight or flight"
- Long term - immune dysfunction, illness
- "stress diathesis model" - developmental implications , endocrine impact on brain vulnerability (Nemeroff, Plotsky)
- Recent proteomics data from the CDC group showing mutations in cortisol regulatory proteins

Depression and immune function and the HPA axis

- Decreases T cell function, NK cell function
- Blunted GH, TRF
- Increased CRF, ACTH, cortisol (as opposed to Demitrack and others finding in CFS)
- Enlarged adrenal mass, pituitary (as opposed to Dinan's findings in CFS)
- When a CFS patient develops depression, what are the neuro-endocrine, immune implications?

Sleep

- Circadian Sleep - Wake neuroendocrine and immune functions in CFS (Modolfsky)
- altered diurnal patterns in cortisol, prolactin
- altered diurnal patterns of NK cell function
- alpha wave intrusion on sleep EEG
- studies associating pro-inflammatory cytokines directly with sleep abnormalities


Conclusion
Immune abnormalities include chronic immune activation and cellular functional defects
CFS as a model for illness caused by neuro - endocrine - immune interactions
Result - Health outcome, termed CFS - cognitive, fatigue, sleep, pain
Significant implications to GWI research