A Primer on ME/CFS

(Myalgic Encephalomyelitis / Chronic Fatigue Syndrome)

A. Martin Lerner, M.D., M.A.C.P.
Beaumont Health System
Treatment Center for Chronic Fatigue Syndrome

Presented by A. Martin Lerner, MD., M.A.C.P., Beaumont Health System, Royal Oak, Michigan August 20, 2011

FOR VIDEO OF THIS PRESENTATION:

VIDEO - PART 1 **VIDEO - PART 2**

Collaborators

- **Antiviral Pharmacodynamics:** R. G. Deeter, PhD, Amgen Corporation
- **Cardiology:** W. O'Neill, M.D., University of Miami, J. Goldstein, M.D., WBH
- **Energy Index Point Score®:** R. G. Deeter, Amgen Corporation
- **Infectious Disease:** M. Zervos, M.D., Henry Ford Hospital
- **Nuclear Medicine:** H. J. Dworkin, M.D., WBH
- **Pathology**: C. H. Chang, M.D., WBH
- **Statistics:** James T. Fitzgerald, PhD, University of Michigan

Collaborators

Continued

- **Dr. A. Martin Lerner CFS Foundation, 2007 – 2011**
  - Ken Gill and Jim Edington, Executive Co-Directors
  - Carol Gill, Executive Committee Member
  - Ann Cavanagh, Communication Director

- **Molecular Virology:** R. Glaser and M. Williams, Ohio State University

- **Molecular Biology:** Safedin Beqaj, PhD, Pathology Inc., Torrence, CA

- **Epidemiology :** L. Jason, PhD, DePaul University

Table of Contents

ME/CFS

Annals of Internal Medicine, Holmes et al, 1988

This is a progressive invalidism.

1) Young healthy, mid-forties, 4 women/1 man; well until becoming ill with a life altering fatigue; continuing, worsening; ultimately unable to work or participate in family activities; unable to shop for groceries; have social activities; confined to bed except for ever shortening periods of time; unable to exercise, worsens all symptoms

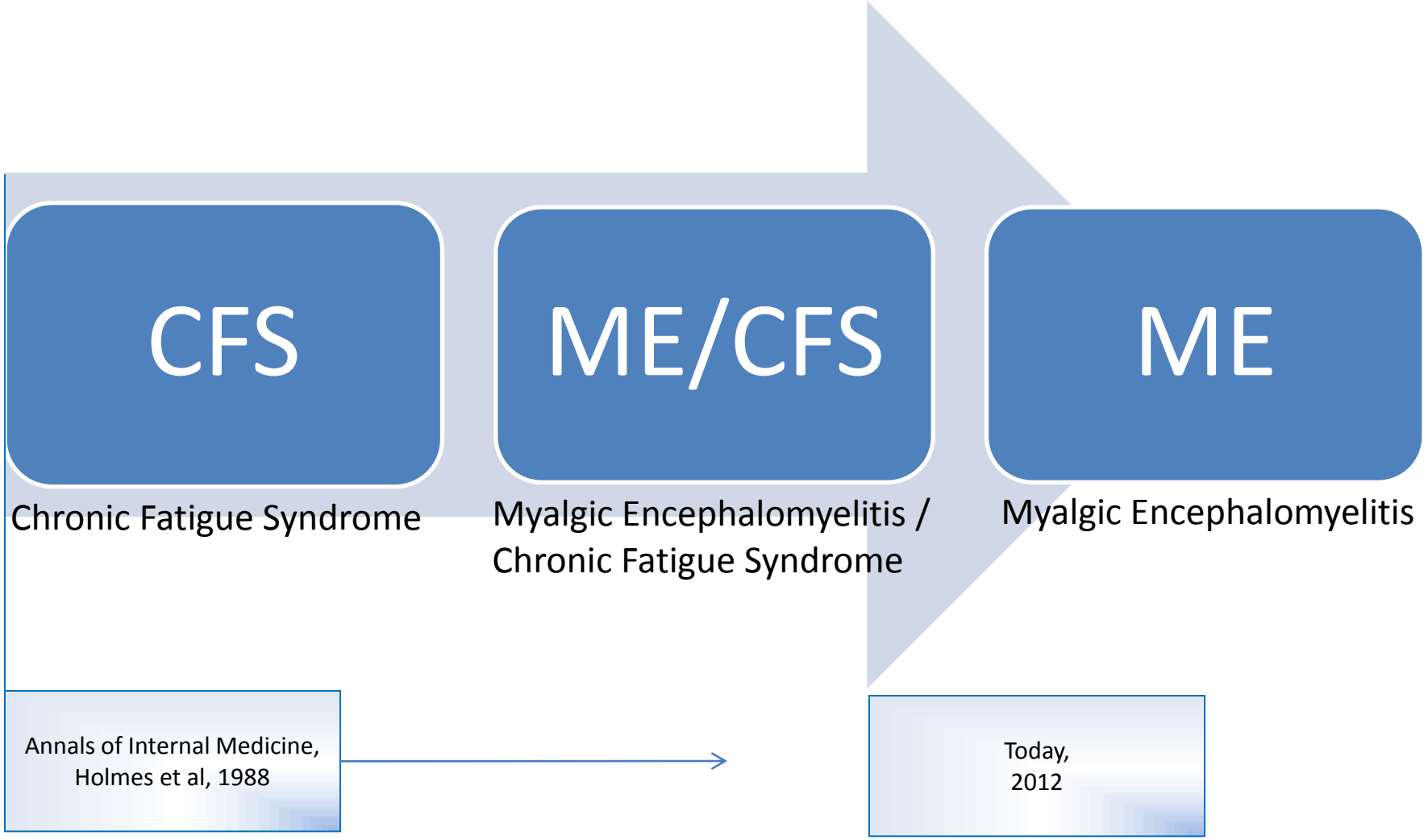
2) Intermittent fevers, syncope, chest pain worsens as day progresses, muscle pain, joint pain, palpitations

ME/CFS

Continued

3) Physical findings:
    a) Early, tachycardia at rest
    b) Cardiomegaly, positive tilt table test, positive Holter monitor
    c) Occasional goiter
4) 20 % die by suicide
5) 20 % die by cardiac failure, in fifth decade
6) Diagnosis - none / ME/CFS
7) Treatment - none
8) ME/CFS patients have been suspected to have psychiatric disease because scientific medicine could make no diagnosis

International Timeline



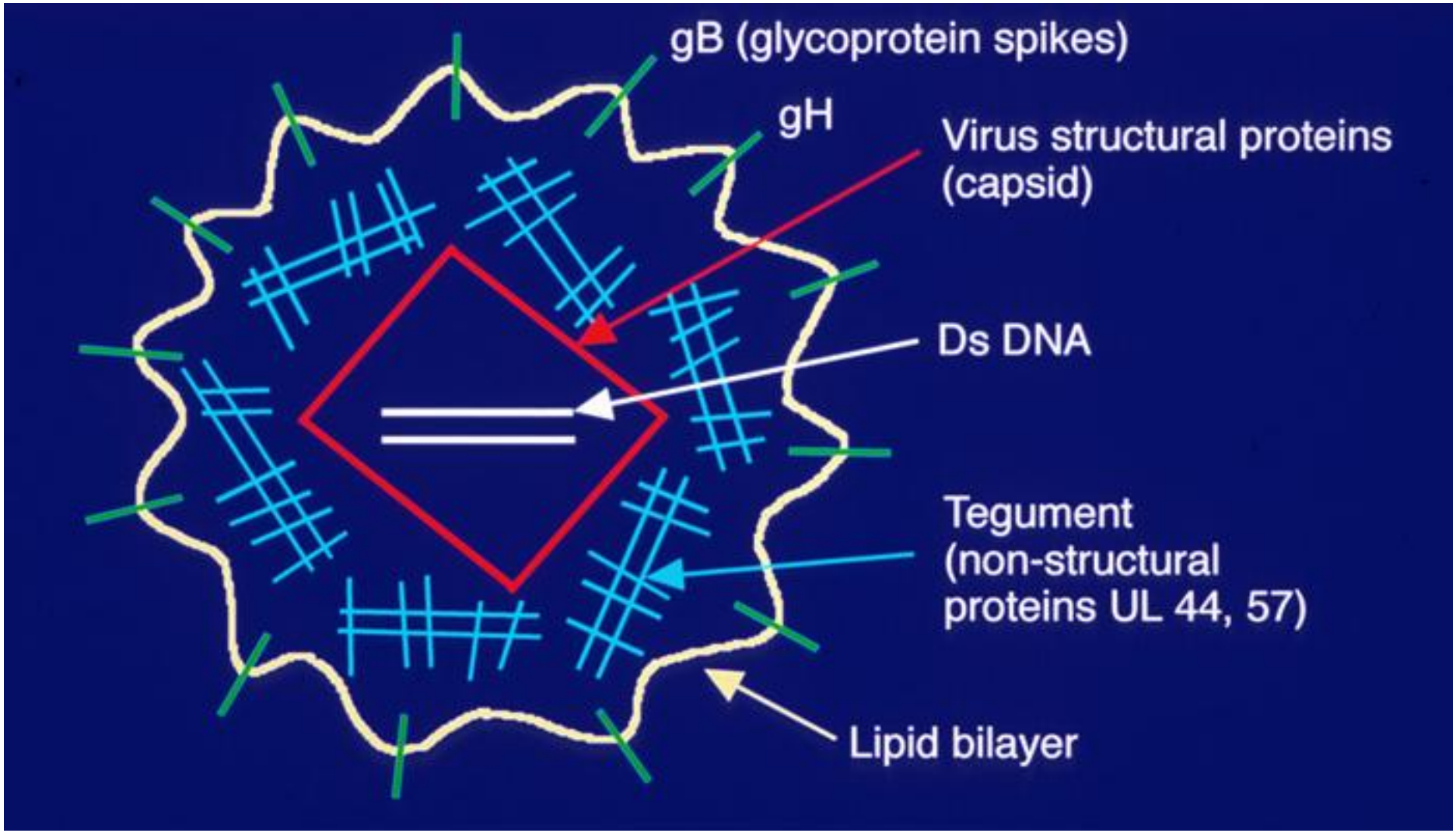
This disease was originally given the name Myalgic Encephalomyelitis(ME). However during the "Incline Village Outbreak" in 1984, the investigative team sent to inspect the situation did not make the connection. In 1988, a new name, Chronic Fatigue Syndrome(CFS), was published in the Annals of Internal Medicine, based on one of the many symptoms common to the illness. Over the following years, the illness became much more well known under this insufficient title CFS. Tired of the inaccurate connotations associated with CFS, the patient/practitioner population started to push back. In an effort to keep the recognition the name CFS had gained, as well as the rights gained in disability legislation, the name was updated to incorporate both ME/CFS. And now, we are beginning to see a big wave of support to push for the original, more legitimate sounding, Myalgic Encephalomyelitis.

I. Virology / Immunology of ME/CFS

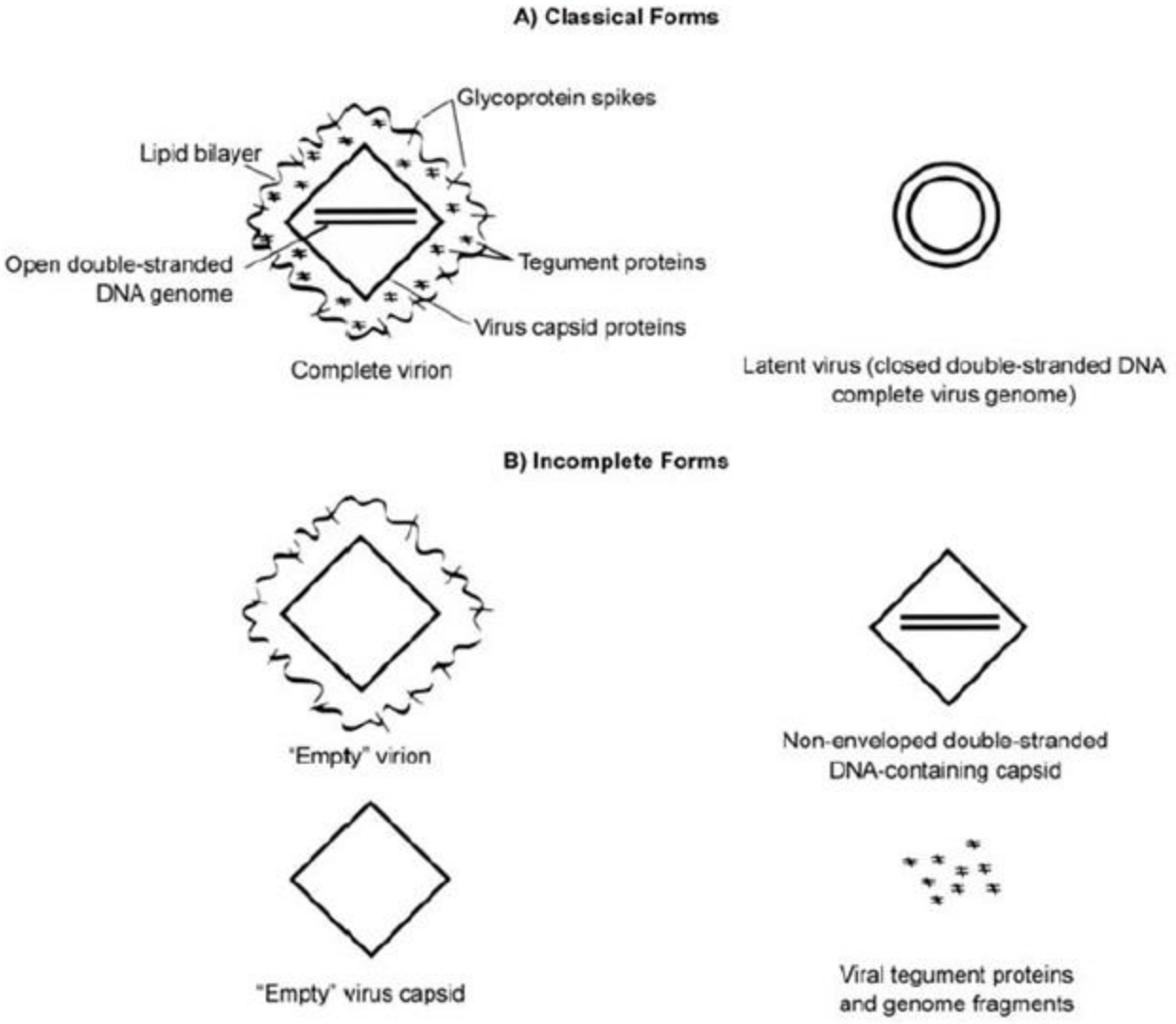
ME/CFS is a New Human Herpesvirus Disease.

Subfamily and Characteristics	Diseases of Lytic Replication
A. Epstein Barr Virus (EBV) growth in epithelial cells, B or T lymphocytes, latent in memory B- lymphocytes	Mononucleosis, myocarditis, hepatitis, meningoencephalitis, thyroiditis
B. Cytomegalovirus (HCMV), latent in monocyte precursors, secretory glands	Mononucleosis, hepatitis, pneumonia, meningoencephalitis
c. Human Herpesvirus 6A, 6B Latent in lymphoreticular cells	Roseola Infantum, mononucleosis, meningoencephalitis

Herpesvirus Complete Virion



Some Forms of Herpesviruses



Herpesvirus Virion

- Enveloped icosahedral (glycoproteins)
- Approximate diameter of enveloped virion, 200nm
- Material between capsid and envelope is tegument (contains at least 14 proteins)
- Genome DNA, double stranded > 100 genes; unique long and short arms, repeat elements and terminal repeat sequences

Herpesvirus Virion

Continued

- Genes express three temporal classes:
  - IE (Immediate Early) – Gene activation
  - E (Early) – DNA replication and late gene activation
  - L (Late) – Virion proteins, regulatory proteins
- Primary Infection – Humoral and cellular immunity to structural virion glycoproteins
- Latent Virus – Closed inactive double stranded episome in nucleus latent cell (HHV6 is integrated in cellular genome.)
- Reactivation – Can occur at any time / especially at times of immunosuppression (e.g. H.I.V., bone marrow organ transplant)
- Latent Replication – Has been associated with malignancy (e.g. Burkitt's lymphoma, Nasopharyngeal carcinoma, Lymphatic Malignancy

Herpesvirus Virion

Continued

- Abortive Lytic replication – Apoptosis ME/CFS
- ME/CFS – Abortive lytic replication – leading to apoptosis with no new Herpesvirus
- Viral genes are sequentially expressed during replication cycle, IE, E, L
- Latent encoded genes are present in EBV-associated malignancy

Hypothesis:

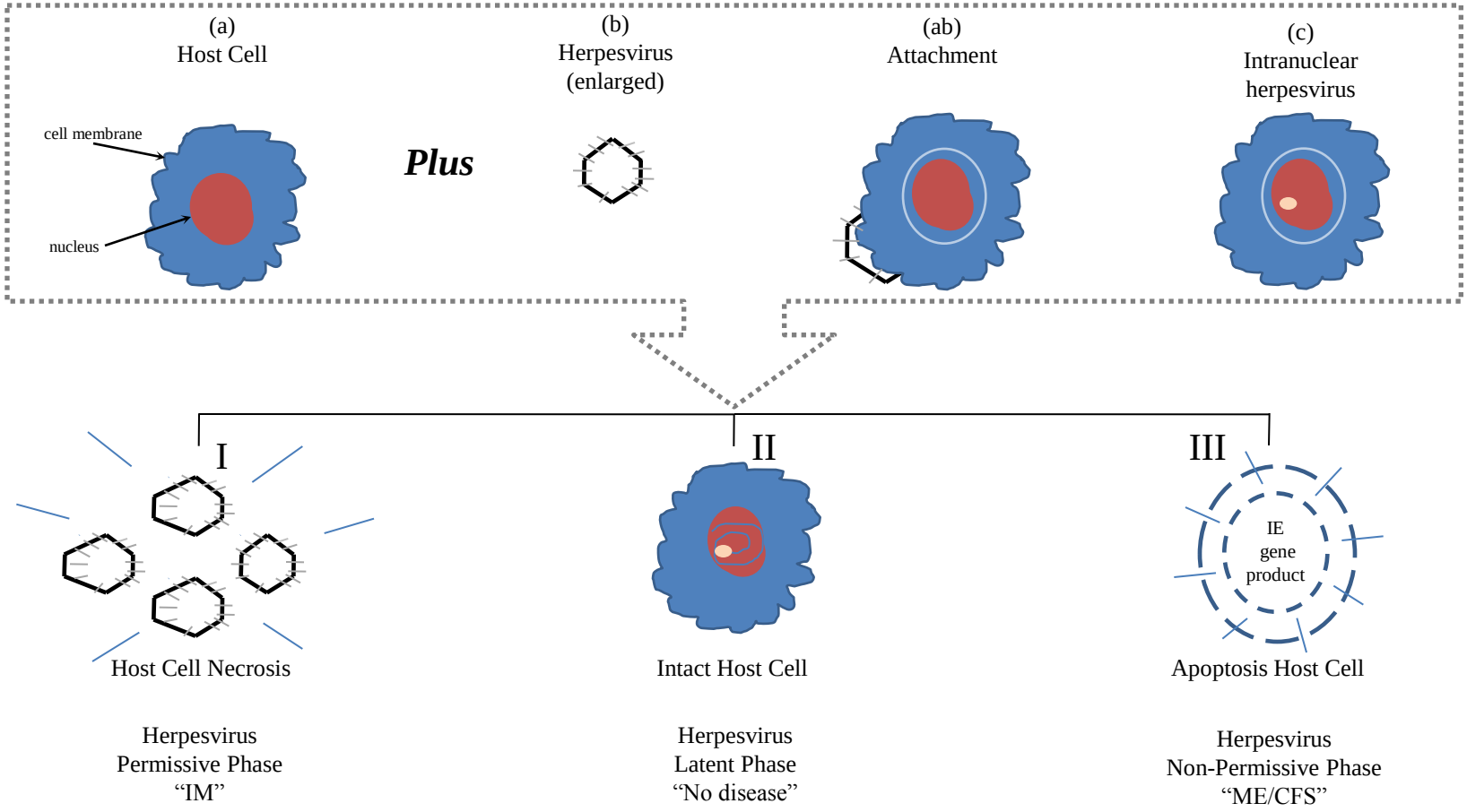
ME/CFS is lytic abortive replication

Herpesvirus Virion

Continued

- In Vitro evidence
  - EBV IE genes without lytic replication produce host cell dysregulation and apoptosis (e.g. peripheral blood mononuclear cells.)
  - IE genes EBV zta, rta and HCMV IE_1, IE_2

Proposed Three Phases of Herpesvirus Replication



During the 3 phases of herpesvirus replication (a) host cell and (b) herpesvirus bind at the cytoplasmic membrane (ab) and (c) herpesvirus transits intranuclearly. Permissive herpesvirus replication yields (I) new virus and host cell necrosis "infectious mononucleosis." (II) The latent herpesvirus phase preserves both the virus genome and the healthy host cell. (III) Non-permissive herpesvirus replication yields host cell apoptosis and no virus, "ME/CFS."

Comparative Herpesvirus Lytic and Abortive Lytic Replication

	Result	Replication	
		Lytic	Abortive Lytic
1	Pathogenic process	Necrosis of host cell, and new infectious virus	Apoptosis of host cell, no new infectious virus
2	Circulation (blood and lymphatics)	EBV (memory B-cell), HCMV (macro-phage, monocyte), HHV6 (T-cell)	None
3	DNA-emia.	Yes	No
4	Antigenemia	Yes	No
5	IgM antibody to complete virus	Yes	No
6	IgM antibody to non-structural gene products.	No	Yes
7	Serum IgG antibody titer to complete virus	Yes increasing	Yes no increase in IgG titer
8	Immediate Early viral gene products	Yes	Yes
9	Activation of Late Viral Gene products	Yes	Uncommon
10	Therapeutic effect of specific EBV, HCMV, HHV6 DNA polymerase inhibitors	Yes (rapid)	“Yes slow” prevents new host cell recruitment (see Figure 1)
11	Proposed therapeutic effect of specific EBV, HCMV, HHV6 inhibitors of immediate early gene products.	Yes (rapid)	"Yes" (rapid)
12	Clinical entities	Infectious mononucleosis, myocarditis, meningoencephalitis, polyneuropathy, thyroiditis: enteritis, pneumonia,retinitis	CFS retinitis, interstitial pneumonia, ME/CFS

Serum Antibodies of Herpesvirus

- EBV, VCA (Viral Capsid Antigen) IgM, IgG
- EBV, EA(D) (Early Antigen Diffuse) - A complex of 30 Early Genes
- EBV, dUTPase
- EBV, DNase
- EBV, DNA polymerase
- HCMV, IgM, IgG
- HCMV, p52 (UL44)
- HCMV CM_2 (UL44 & UL57)
- HHV6, IgM, IgG

II. ME/CFS Pathologic Physiology

1) Abnormal Holter Monitoring Oscillating T-wave Flattening and Inversions

2) Tachycardia at Rest

3) Left Ventricular (LV) Dilatation

4) Decreased LV Ejection Fraction

5) Pathologic / Cardiomyopathy / Apoptosis (Lytic Replication Produces Myocarditis with Cellular Inflammatory Response)

6) Reversible by Subset-directed Antiviral Therapy, If Treatment Begun Promptly

MUGA Rest/Stress Studies in CFS Patients with Left Ventricular Dysfunction

Pat. No.	Date of Test	Cardiac Wall Motion	Ejection Fraction		Maximum Stress
			Rest	Stress	
1	2/01/88	-	45%	-	-
	3/10/88	diffuse slight hypokinesis at stress	66%	52%	-
	1/18/90	biventricular dilatation at stress	59%	52%	600
	5/20/93	biventricular dilatation at stress	58%	52%	600
2	8/08/91	inferior apical hypokinesis at stress	63%	53%	600
	3/13/92	tardokinesis at apical region which increases with stress	50%	36%	600
3	7/20/92	-	46%	55%	400
4	10/12/93	-	40%	56%	1000
5	11/28/95	severe hypokinesis of posterior basal wall at both rest and stress	66%	72%	600

Reference: Clin. Nuclear. Med. 1994: 19; 657-677

Sequential Holter Monitoring of a 31-year-old Woman with CFS

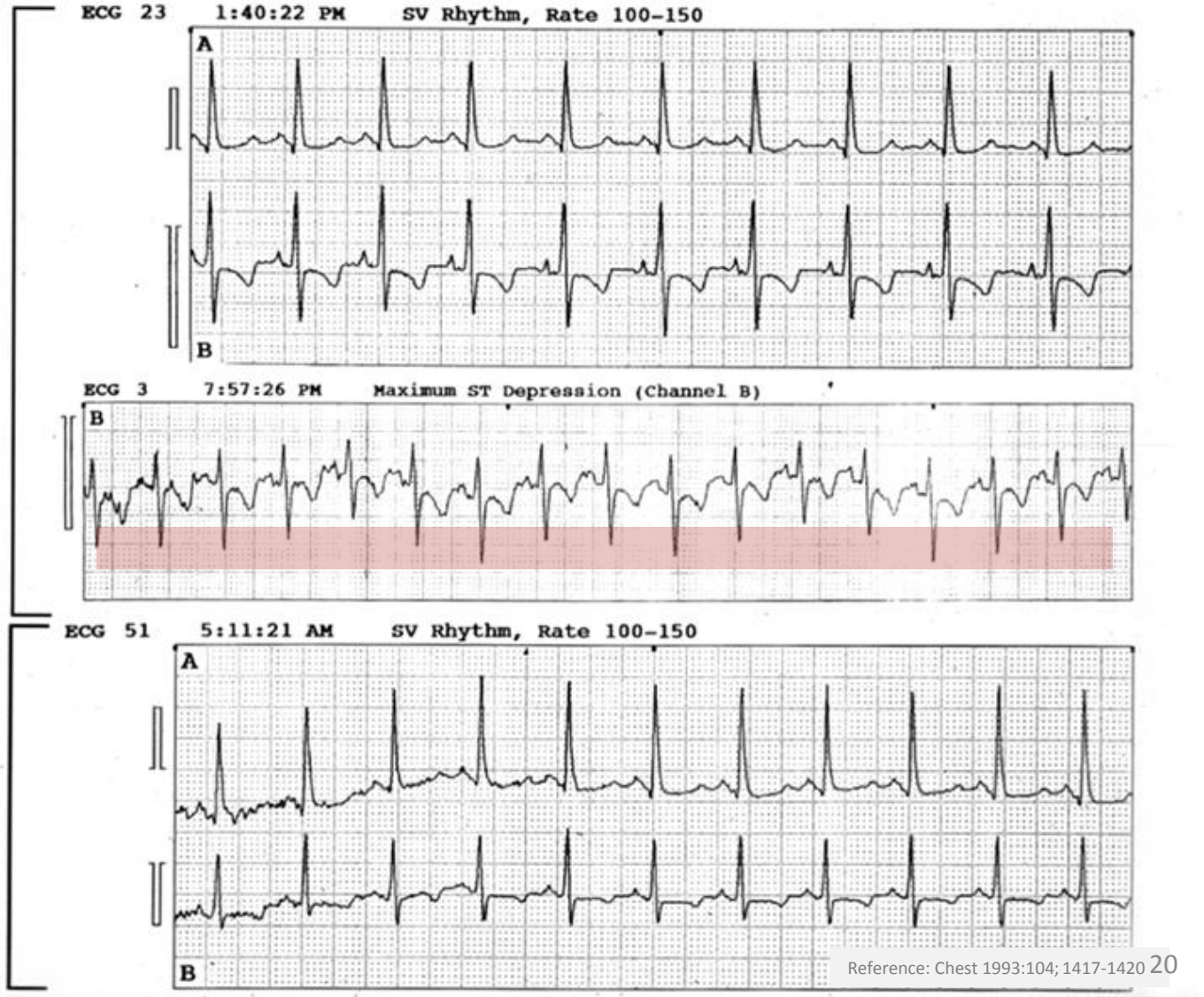
Before Valacyclovir Therapy

May 11, 1996

January 7, 1997

After Valacyclovir Therapy

October 17, 1997

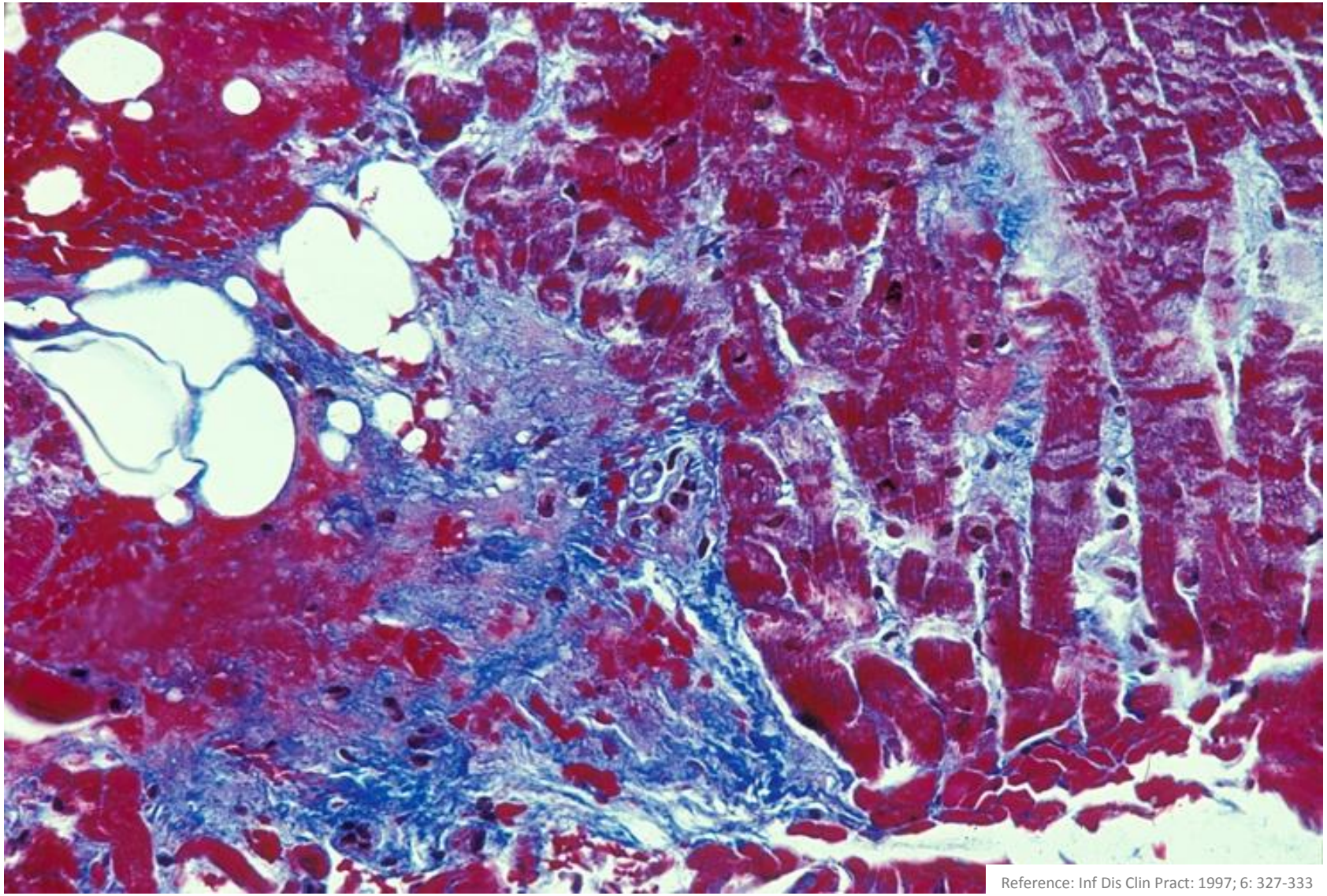


Reference: Chest 1993:104; 1417-1420

Incidence of T-Wave Inversions and T-Flats

Number of Patients	CFS (51)	Non-CFS (77)	p Value
T-wave inversions	61%	34%	<0.01
T-flats	96%	71%	<0.01

Cardiomyopathy (Biopsy) in HCMV CFS (fibrosis, myofiber disarray, fatty infiltration)



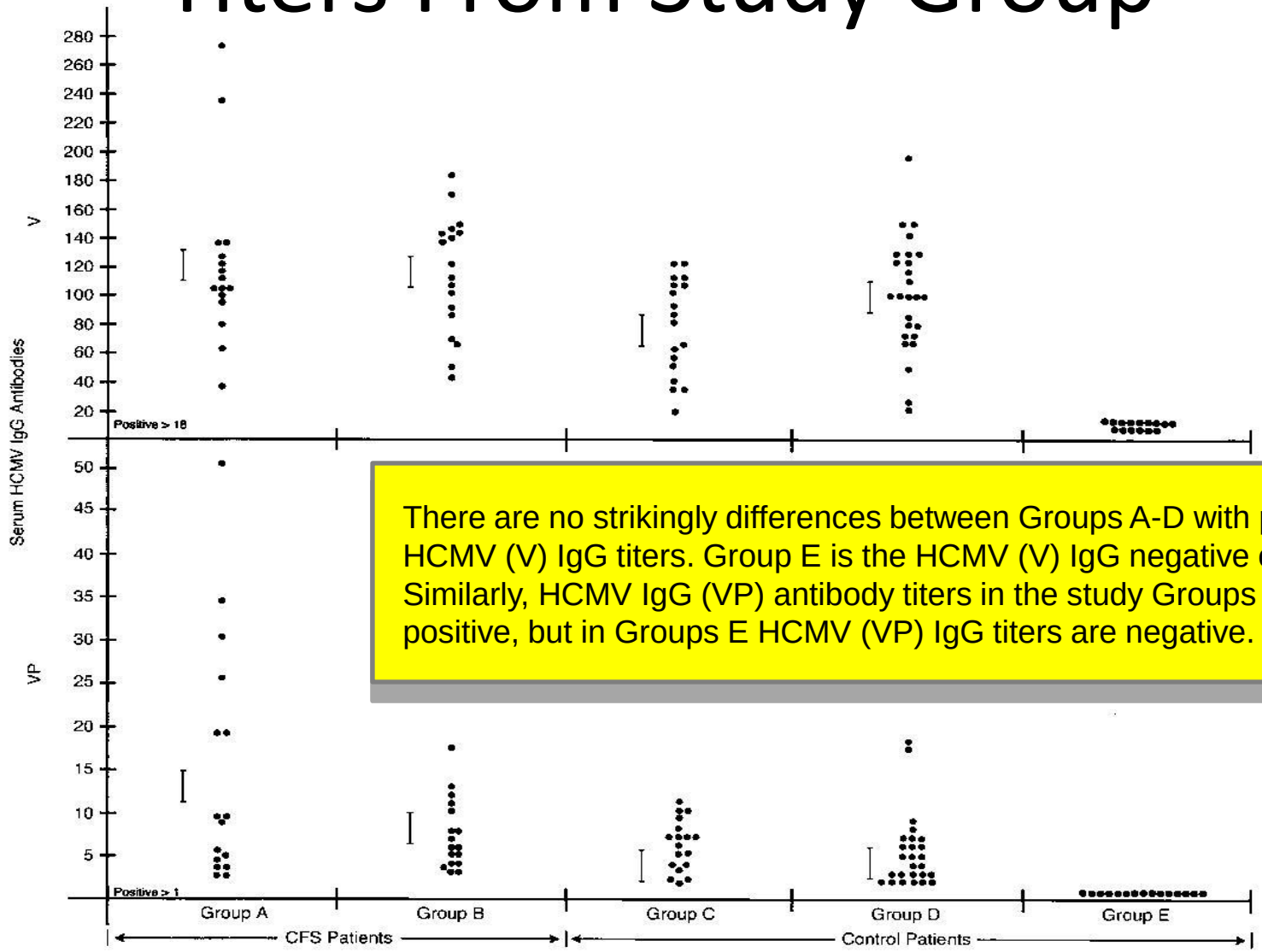
Reference: Inf Dis Clin Pract: 1997; 6: 327-333

Demographics of 98 CFS Patients in Birmingham, Michigan 1987 – 1994

Variable	All CFS Patients*	CFS Patients with abnormal stress MUGAs (21)	CFS Patients with Normal stress MUGAs (66)	Significance
Age, years, mean	42.3±10.6	45.2±11.0	41.6±9.5	NS+
Women %	87%	81%	91%	NS
Duration of CFS (months)	12.2±11.3 (80)	9.6±6.3 (15)	12.6±11.1 (65)	NS
Other medical diagnoses %	21%	32%	15%	NS
Diabetes mellitus %	0%			NS
Hypertensive vascular disease %	3%	0%	4%	NS
Total cholesterol > 250 mg%	12%	19%	8%	NS
Obesity %	6%	6%	8%	NS
Cigarette smokers	16%	20%	13%	NS
Alcohol %				
1. Non-user	43%	40%	44%	NS
2. 1 or 2/mos **	37%	45%	36%	
3. 1 or 2/wk	12%	5%	13%	
4. 1 or 2/day	7%	5%	7%	
5. 3+/day	1%	5%	0%	
Antidepressants at first visit	11%	0%	15%	NS

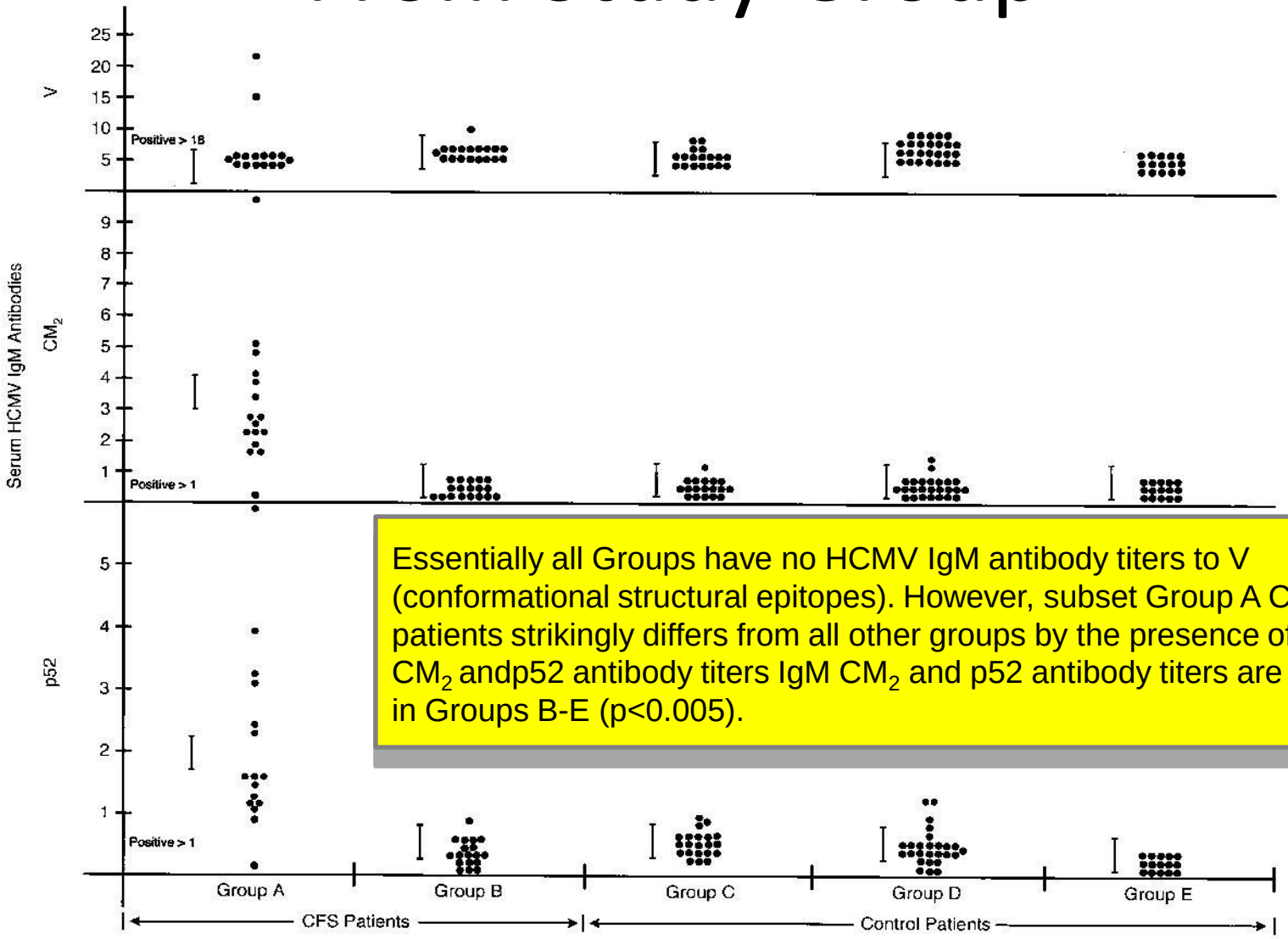
*The number of CFS patients evaluated is listed in parenthesis.
**One jigger equals 45cc alcoholic beverage
+NS, not significant

Serum HCMV IgG (V) Antibody Titers From Study Group



There are no strikingly differences between Groups A-D with positive HCMV (V) IgG titers. Group E is the HCMV (V) IgG negative control. Similarly, HCMV IgG (VP) antibody titers in the study Groups A-D are positive, but in Groups E HCMV (VP) IgG titers are negative.

Serum HCMV IgM Antibody Titers From Study Group



Essentially all Groups have no HCMV IgM antibody titers to V (conformational structural epitopes). However, subset Group A CFS patients strikingly differs from all other groups by the presence of IgM CM_2 andp52 antibody titers IgM CM_2 and p52 antibody titers are negative in Groups B-E ($p<0.005$).

Conclusion
ME/CFS Virology Immunology

ME/CFS is Herpesvirus (EBV, HCMV, HHV6) as single or multiple abortive lytic replication.

III. ME/CFS Diagnosis & Treatment

Energy Index Point Score®
Functional Capacity Criteria

0	Bed-ridden, up to bathroom only
1	30 minutes – 1 hour daily out-of-bed (sitting in chair, is out of bed)
2	Out of bed – over 30 min. to 2 hrs/day
3	Out of bed – 2 – 4 hrs/day
4	Out of bed – 4 – 6 hrs/day
5	Can work at sedentary job, 40 hrs/week with difficulty

Recovery

6	Daily naps in bed, may maintain a 40 hr. sedentary work week plus light, limited housekeeping and/or social activities
7	No naps in bed. Up 7:00 a.m. to 9:00 p.m. Able to work a sedentary job plus light housekeeping.
8	No naps. Able to manage full work (sedentary) plus manage a household.
9	May exercise at approximately 1/2 - 2/3 normal without excessive fatigue.
10	Normal

Reference: In Vivo 2008:22; 799-802

Diagnostic Panel for Group and Subset Classification of ME/CFS

1. International criteria for CFS
2. 24-hour ECG monitor
3. Tachycardia at rest
4. Elevated serum Epstein-Barr virus (EBV), Early Antigen (D) ± elevated serum viral-capsid antigen IgM
5. Elevated serum antibody titer cytomegalovirus (HCMV), IgG
6. Elevated serum antibody titer Herpesvirus 6 IgG
7. *Serum Borrelia burgdorferi, Western blot, IgM and IgG: ELISA IgM and IgG
8. *Serum Babesia microti IgG
9. *Serum Anaplasma phagocytophilia, IgG
10. *Serum Mycoplasma pneumoniae, < 600 IgG
11. *Serum Antistreptolysin 0, <400

Note: Group A ME/CFS requires criteria 1, 2, and, elevated serum IgG antibody titers to one or several of EBV, HCMV, or HHV6 IgG herpesviruses. Group B ME/CFS requires criteria 1, 2, elevated serum IgG antibody titers to one or several of EBV, HCMV or HHV6 herpesviruses plus co-infection one or more criteria 7 – 11.

Physician Treatment

- Patient Visits Every 4-6 weeks
- EIPS®– Collaboration (patient & physician)
- Physical examination
- Syncope, tachycardia at rest (Most common findings)
- Laboratory

  CBC, AST, ALT, CBS, urinalysis, ECG

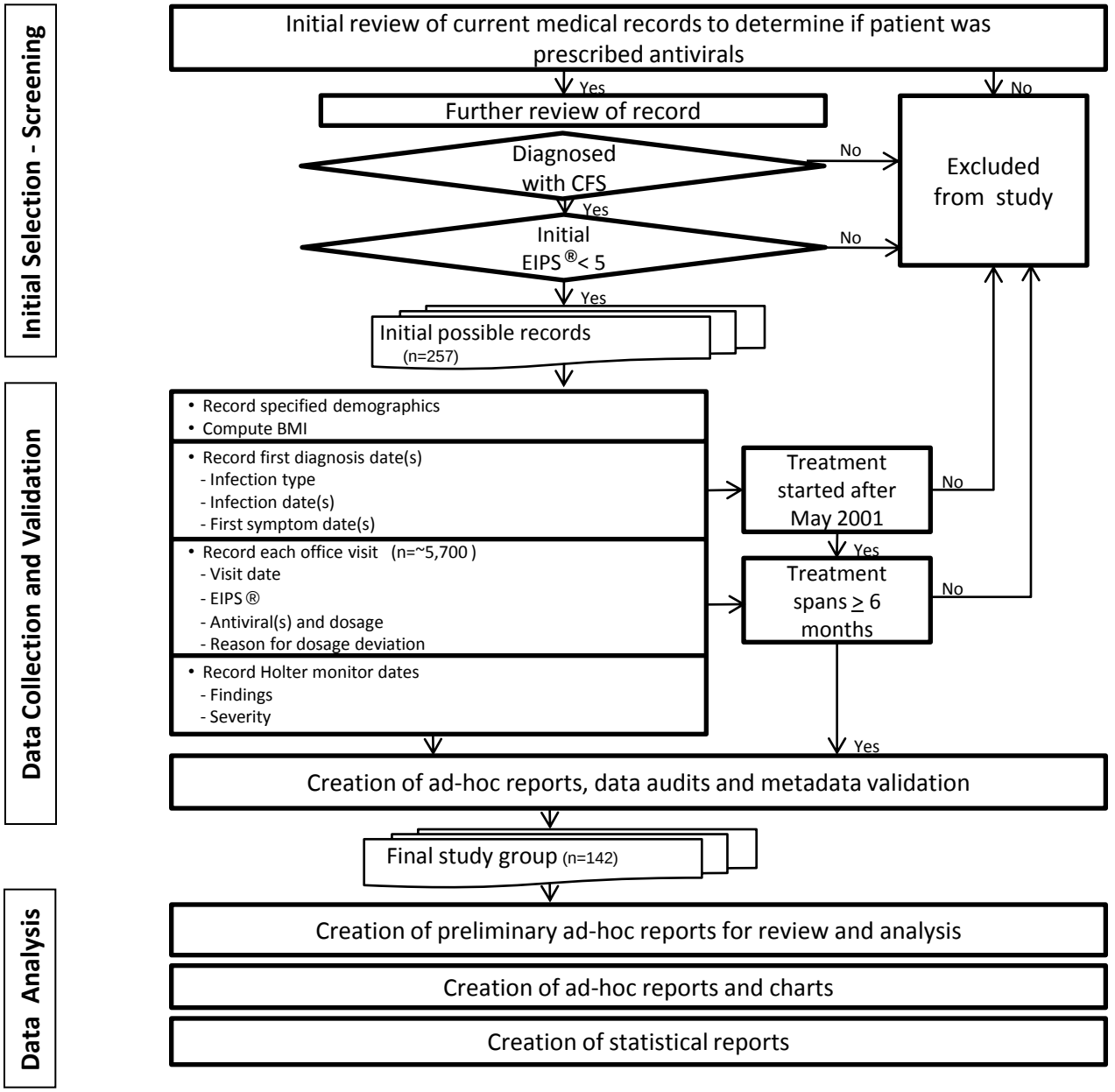
  (EBV, HCMV, HHV6 titers every 3 months)

Note: Initial Jarisch-Herxheimer response; Little or no improvement for 6 months

CFS Chart Study - Data Collection

- Our CFS Foundation began a systematic review of all patients at my treatment center between 2001 and 2007.
- With an identical diagnostic protocol for 6 years, a detailed chart study of 257 CFS patients was conducted. This included over 7,000 patient visits and over 35,000 fields of data.
- We present data from this systematic review of 142 CFS patients from one clinic, with single physician visits every 4-6 weeks (for a minimum duration of $\geq$ 6 months).

Data Collection: Process Flow Chart



Demographics of 142 Patients with CFS, 2001-2007

Patients	Group A patients (n = 106)	P value	Group B		Patients without B.b. (n = 10)
			All patients (n = 36)	B.b. (n = 26)	
Women	77 patients (73%)		28 patients (77.8%)	23 patients (63.8%)	5 patients (13.9%)
Men	29 patients (27%)		8 patients (22.2%)	3 patients (8.3%)	5 patients (13.9%)
Age, all patients (mean ± SEM)	46.2 + 1.3 years				
Age, women	47.1 ± 1.5 years	0.309[1]	44.2 years	44.5 years	43 years
Age, men	44.0 ± 2.8 years		40.9 years	48.3 years	36.4 years
BMI, all patients (mean ± SEM)	26.4 ± 0.5 kg/m^2		26.5 kg/m^2	26.8 kg/m^2	25.7 kg/m^2
BMI, women	26.6 ± 0.6 kg/m^2	0.573[1]	26.4 kg/m^2	26.9 kg/m^2	24.1 kg/m^2
BMI, men	26.0 ± 0.6 kg/m^2		26.7 kg/m^2	26 kg/m^2	27.1 kg/m^2
All patients duration of illness (mean ± SEM prior to treatment)	4.8 ± 0.5 years		5.9 years	4.7 years	8.9 years
Duration of illness prior to 1st antiviral treatment, women	4.6 ± 0.6 years	0.537[1]	4.5 years	4.1 years	6.1 years
Duration of illness prior to 1st antiviral treatment, men	5.3 ± 1.2 years		10.8 years	9.5 years	11.6 years
All patients duration of antiviral treatment (mean ± SEM)	2.4 ± 0.2 years		2.6 years	2.6 years	2.4 years
Duration of antiviral treatment, women	2.5 ± 0.2 years	0.416[1]			
Duration of antiviral treatment, men	2.2 ± 0.3 years				
All patients baseline EIPS, (mean ± SEM)	4.2 ± 0.1		3.8	4.0	3.4
Baseline, EIPS, women	4.2 ± 0.1	0.695[1]			
Baseline, EIPS, men	4.3 ± 0.2				
All patients last EIPS, patients (mean ± SEM)	6.1 ± 0.2		5.3	5.4	5.0
Last EIPS, women	6.0 ± 0.2	0.329[1]			
Last EIPS, men	6.3 ± 0.3				
All patients delta*, (mean ± SEM)	1.9 ± 0.2	<0.0001[2]	1.5	1.5	1.9
Delta*, women	1.8 ± 0.2	0.378[1]			
Delta*, men	2.1 ± 0.3				

Abbreviations: B.b., *Borrelia burgdorferi; EIPS®, Energy Index Point Score®; CFS, chronic fatigue syndrome; SEM, standard error of measurement; BMI, body mass index.*
1t-test (two-tailed) to determine differences between men and women; 2paired t-test (two-tailed) to determine difference between baseline and last EIPS; *last EIPS minus first EIPS. Group B patients have multiple coinfections. Data listed are mean values.

Single and Multiple Herpesvirus Subsets in Group A CFS Patients

	Women (n)	Men (n)	Total patients
Single herpesvirus CFS			
EBV	20	10	30 (28.3%)
HCMV	8	5	13 (12.3%)
HHV6	2	0	2 (1.9%)
Total	30	15	45 (42.5%)
Pearson Chi-square $P = 0.562$			
Multiple herpesvirus CFS			
EBV/HCMV	24	6	30 (28.3%)
EBV/HCMV/HHV6	7	5	12 (11.3%)
EBV/HHV6	11	3	14 (13.2%)
HCMV/HHV6	5	0	5 (4.7%)
Total	47	14	61 (57.5%)
Pearson chi-square $P = 0.258$			

Abbreviations: EBV, Epstein-Barr virus; HCMV, cytomegalovirus; HHV6, human herpesvirus 6; CFS, chronic fatigue syndrome.

Antiviral Treatment

- Group A
  - EBV treated with Valacyclovir
    - 1 gm every 6 hours(given patient weighed > 79.5kg), 6 glasses of water required
  - HCMV/HHV6 treated with Valganciclovir
    - 450mg in the morning with food for 3 days, increase to 900mg in morning with food for 3 days, finally add 450mg 12 hours later; if elevated aminotransferase(s) occurred, Valganciclovir held until serum transaminases were normal; then return to 900mg per day
- Group B
  - EBV treated with Valacyclovir as in Group A
  - HCMV/HHV6 treated with Valganciclovir as in Group A
  - Co-infections treated with antibiotics

Reference: Virus Adaptation and Treatment 2010: 2:;1-11

Therapy / EBV

1) Valacyclovir (Glaxo-Welcome, TEVA) (Valtrex)
   a) 14.3 mg/Kg pc q6h, wt. $\leq$ 80Kg
   b) ID_{50} EBV $\leq$ 3 mcg/ml
   c) Probenecid 0.5gm B.I.D.
   d) Cimetidine 400mg B.I.D.

   } ↑ Area under curve

   e) EBV DNA polymerase. Thymidine Kinase
   f) Toxicity – Valacyclovir / Acyclovir renal calculi
   g) Occasional diarrhea
   h) ↑MCV, not a toxicity to be concerned about

Therapy / EBV

Continued

2) Famciclovir (Famvir)
    a) Dosage similar to Valacyclovir
    b) ID_{50} EBV equivalent to valacyclovir, higher intracellular concentrations
3) Jarisch-Herxheimer response 2-4 weeks at initiation of therapy
4) Treatment trial 1 year: Response $\geq$ 6 months

Therapy / HCMV / HHV6

1) Valganciclovir - Valcyte
    a) 450 mg, 2qAM, 2nd PM dosing prn
    b) ID_{50} HCMV/HHV6 $\leq$ 0.1 mcg/ml
    c) HCMV/HHV6 DNA polymerase
    d) Toxicity – hepatotoxicity, has caused liver cancer in experimental murine model
2) Others, Leflunomide (Arava) 10 mg 1-2 x 1d
3) Valacyclovir – UL_{97}
4) Cidofovir – Strict IV protocol to avoid severe nephrotoxicity. IV Rx q 12d

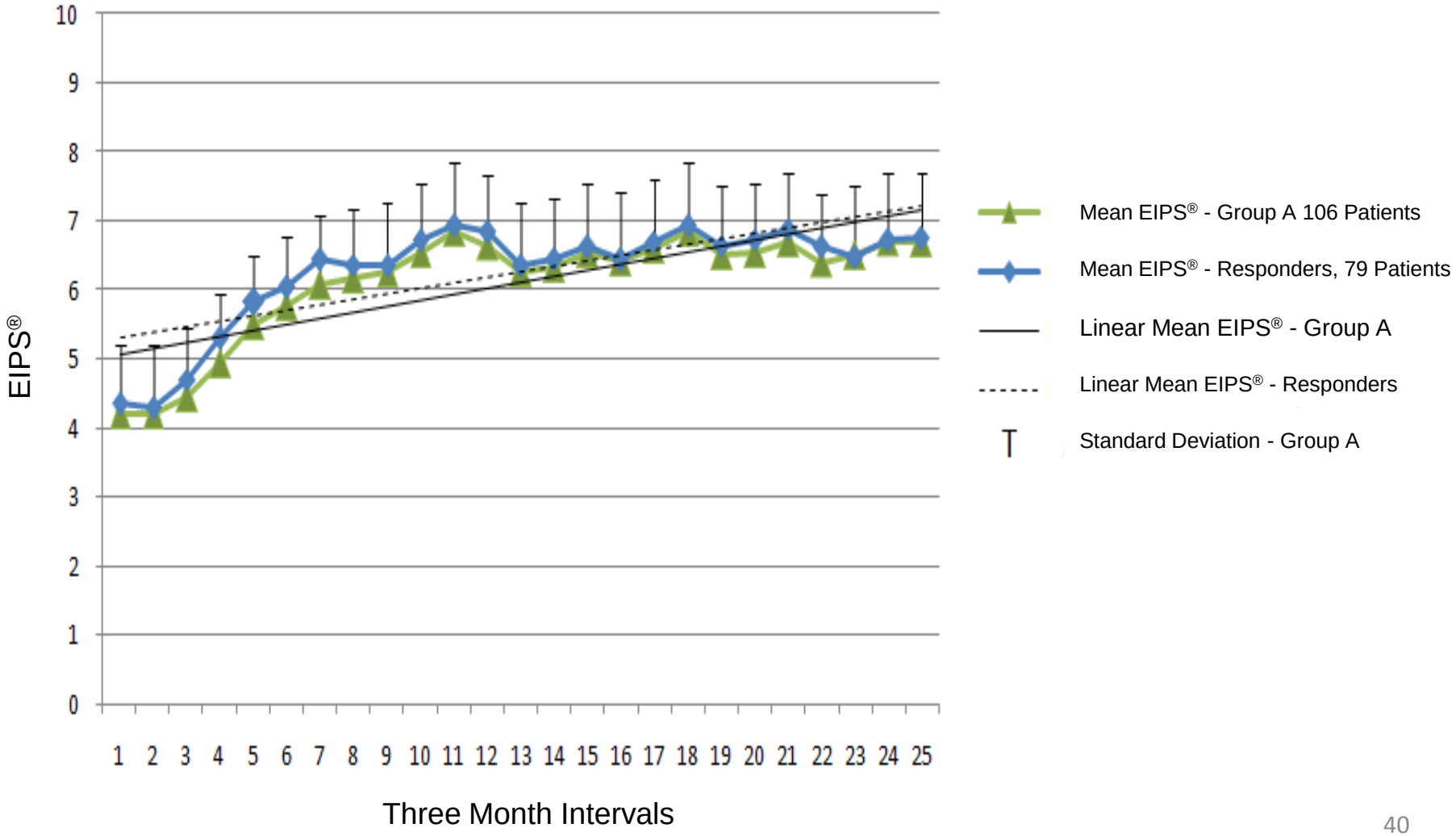
Demographics of 106 Group A Herpesvirus CFS Patients, 2001-2007, "Responders and Non-responders*"

	Responders	Non-responders	p-value
Number of Patients	79	27	
Females	58	19	0.805[1]
Males	21	8	
Age (years)	45.5	48.4	0.347[2]
BMI (kg/m^2)	26.1	27.2	0.353[2]
Mean duration of CFS prior to antiviral therapy (years)	3.9	7.3	0.005[2]
Single Herpesvirus Subset (patients)	33 (41.7%)	12 (44.4%)	0.825[1]
Multiple Herpesvirus Subset (patients)	46 (58.3%)	15 (55.6%)	
Mean duration of antiviral therapy (years)	2.70	1.53	0.001[2]
Mean first EIPS®	4.34	3.81	0.006[2]
Mean last EIPS®	6.88	3.73	<0.001[2]
Difference, EIPS® associated with antiviral therapy	2.54	-0.08	<0.0001[3]

[1] Fisher's Exact Test (2-Tail)
[2] t Test (2-Tail)
[3] Multivariate analysis of variance with repeated measures

* A responder is a patient whose EIPS increases by at least one EIPS unit. A non-responder is a patient whose EIPS did not increase by at least one EIPS unti.

Improvement in EIPS® 106 Group A CFS Patients after Antiviral Therapy



Mean EIPS® at Three-month Intervals for 106 Group A CFS Patients Including 79 (74.5%) Group A "Responders"

Total Group A - 106 Patients

3 Month Intervals	Number of Patients	Mean of EIPS	Standard Deviation of EIPS
0	106	4.21	0.87
1	98	4.19	0.95
2	104	4.44	1.21
3	103	4.94	1.49
4	96	5.49	1.50
5	84	5.77	1.47
6	78	6.06	1.46
7	66	6.17	1.38
8	59	6.25	1.25
9	51	6.55	1.05
10	47	6.83	1.15
11	46	6.65	1.24
12	40	6.26	1.40
13	38	6.32	1.46
14	38	6.54	1.36
15	33	6.42	1.19
16	30	6.59	1.20
17	28	6.83	1.21
18	27	6.52	1.40
19	22	6.55	1.48
20	18	6.69	1.86
21	14	6.40	1.47
22	13	6.51	0.89
23	13	6.70	0.88
24	6	6.70	1.32

Group A "Responders" - 79 Patients

3 Month Intervals	Number of Patients	Mean of EIPS	Standard Deviation of EIPS
0	79	4.36	0.80
1	75	4.29	0.93
2	77	4.70	1.19
3	76	5.30	1.47
4	73	5.84	1.40
5	68	6.03	1.37
6	65	6.44	1.24
7	57	6.37	1.25
8	53	6.35	1.20
9	46	6.71	0.82
10	44	6.94	0.98
11	42	6.84	0.97
12	37	6.35	1.33
13	35	6.44	1.39
14	36	6.63	1.32
15	31	6.45	1.18
16	28	6.70	1.03
17	26	6.94	1.10
18	25	6.64	1.34
19	20	6.74	1.31
20	16	6.89	1.74
21	12	6.64	1.40
22	12	6.47	0.92
23	12	6.72	0.92
24	5	6.88	1.49

Reference: Virus Adaptation and Treatment 2010: 2 1-11

Mean EIPS® at Three-month Intervals for 106 Group A CFS Patients Including 79 (74.5%) Group A "Responders"

Total Group A - 106 Patients				Group A "Responders" - 79 Patients			
3 Month Intervals	Number of Patients	Mean of EIPS	Standard Deviation of EIPS	3 Month Intervals	Number of Patients	Mean of EIPS	Standard Deviation of EIPS
0	106	4.21				4.36	0.80
1	98	4.19				4.29	0.93
2	104	4.44				4.70	1.19
3	103	4.94				5.30	1.47
4	96	5.49				5.84	1.40
5	84	5.77				6.03	1.37
6	78	6.06				6.44	1.24
7	66	6.17				6.37	1.25
8	59	6.25				6.35	1.20
9	51	6.55				6.71	0.82
10	47	6.83				6.94	0.98
11	46	6.65				6.84	0.97
12	40	6.26				6.35	1.33
13	38	6.32				6.44	1.39
14	38	6.54				6.63	1.32
15	33	6.42				6.45	1.18
16	30	6.59				6.70	1.03
17	28	6.83				6.94	1.10
18	27	6.52				6.64	1.34
19	22	6.55				6.74	1.31
20	18	6.69				6.89	1.74
21	14	6.40				6.64	1.40
22	13	6.51				6.47	0.92
23	13	6.70				6.72	0.92
24	6	6.70				6.88	1.49

Increase of Mean EIPS® from 4.21 to a high of 6.70.

From only 4-6 hrs out of bed to a full time job!

Reference: Virus Adaptation and Treatment 2010: 2 1-11

Demographics: 106 Group A CFS Patients

	Number of Patients	p-value
Females	77 patients (73%)	
Males	29 patients (27%)	
Age, 106 patients (Mean ± SEM)	46.2 + 1.3 years	
Age, females	47.1 ± 1.5 years	0.309[1]
Age, males	44.0 ± 2.8 years	
BMI, 106 patients (Mean ± SEM)	26.4 ± 0.5 Kg/m^2	
BMI, females	26.6 ± 0.6 Kg/m^2	0.573[1]
BMI, males	26.0 ± 0.6 Kg/m^2	
Duration of illness (Mean ± SEM) prior to treatment, 106 patients	4.8 ± 0.5 years	
Duration of illness prior to 1st antiviral treatment, females	4.6 ± 0.6 years	0.537[1]
Duration of illness prior to 1st antiviral treatment, males	5.3 ± 1.2 years	
Duration of antiviral treatment (Mean ± SEM)	2.4 ± 0.2 years	
Duration of antiviral treatment, females	2.5 ± 0.2 years	0.416[1]
Duration of antiviral treatment, males	2.2 ± 0.3 years	
Baseline "EIPS®", 106 patients (Mean ± SEM)	4.2 ± 0.1	
Baseline, "EIPS®", females	4.2 ± 0.1	0.695[1]
Baseline, "EIPS®", males	4.3 ± 0.2	
Last "EIPS®", 106 patients (Mean ± SEM)	6.1 ± 0.2	
Last "EIPS®", females	6.0 ± 0.2	0.329[1]
Last "EIPS®", males	6.3 ± 0.3	
Delta*, 106 patients (Mean ± SEM)	1.9 ± 0.2	< 0.0001[2]
Delta*, females	1.8 ± 0.2	0.378[1]
Delta*, males	2.1 + 0.3	

[1] t Test (2-tail) to determine differences between men and women

[2] Paired t Test (2-tail) to determine difference between baseline and last "EIPS®"

* Last "EIPS®" minus first "EIPS®"

Reference: Virus Adaptation and Treatment 2010: 2 1-11

142 CFS Patient Systematic Review

- EIPS® values increased significantly
- Cardiac, immunologic, and neurocognitive abnormalities improved and/or disappeared
- 106 CFS patients (Group A EBV, HCMV, HHV6 in single or multiple infection with no co-infections)
  - Treated with subset-directed antiviral nucleosides, valacyclovir and valganciclovir and returned to sustain normal lives.
- 36 CFS patients (Group B EBV,HCMV, HHV6 with co-infections)
  - In addition to antiviral treatment, required antibiotic treatment for co-infections; improvement occurred, but not as markedly successful as Group A

Suggestions – Group B

1) Duration of therapy, not established
2) Rheumatic Fever / my method Dx_ASO $\geq$ 400 plus Holter abnormalities
    a) IV unasyn 3 gm q 8 hr 30d, then
    b) Bicillin 2.4u 1M q 14 days until ASO titer $\leq$ 200
    c) If enlarged tonsils, tonsillectomy
3) Mycoplasma pneumoniae Lab Corp IgG 2x > / my method
    a) Rx: doxycycline IV or po 100,150mg q 12h. Moxifloxacin 400mg 1-(2) x 1d, depending on weight
    b) Duration, until IgG Mycoplasma pneumoniae, negative
4) Babesiosis, Ehrlichiosis – po Rx per ID Society guidelines at least 30 d

Therapy / Care-Points

1) Care: Valacyclovir - must drink $\geq$ 6 8 oz. glasses water 1d to avoid renal stones, obstruction
2) Care: Valcyte - $\uparrow$ AST, ALT Do not tolerate any increase
3) No response 1st 6 months
4) Treatment trial $\geq$ 12 months
5) Prognosis:
    I. Younger patients
    II. Shorter period of illness before beginning antiviral Rx
    III. Higher baseline EIPS ®
6) The higher IgG EBV, HCMV, HHV6, the greater is the viral load.

Conclusion

1) Antiviral Nucleosides valacyclovir (EBV) and valganciclovir (HCMV, HHV6) inhibit Herpesvirus Host-cell necrosis (new virus replication) and Host-cell apoptosis (IE gene expression).
2) Causal relationship between CFS and EBV/HHV6/HCMV, specifically abortive lytic EBV/HHV6/HCMV replication producing host-cell apoptosis.
3) Previous research has not proven antiviral success due to limited timelines (6 months or less), and lack of subset classification of CFS patients.

Conclusion

Continued

4) Long term group and subset directed antiviral treatment is successful!

5) **ME/CFS patients return to more normal lives - work, raise families and socialize.**