

# Successful Antiviral Treatment of Chronic Fatigue Syndrome and Its Science

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# Collaborators

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- **Energy Index Point Score<sup>®</sup>:** R. G. Deeter, Amgen Corporation
- **Infectious Disease:** M. Zervos, Henry Ford Hospital
- **Nuclear Medicine:** H. J. Dworkin, WBH
- **Pathology:** C. H. Chang, WBH
- **Statistics:** James T. Fitzgerald, University of Michigan

CFSLLC owns patents for diagnosis and treatment of CFS with antiviral agents.

# Order of Presentation

- Introduction
- CFS Chart Study
  - Data Collection
  - CFS Group & Subsets
  - Energy Index Point Score®
  - Schedule
  - Demographics
  - Results
- The Science
- Conclusion

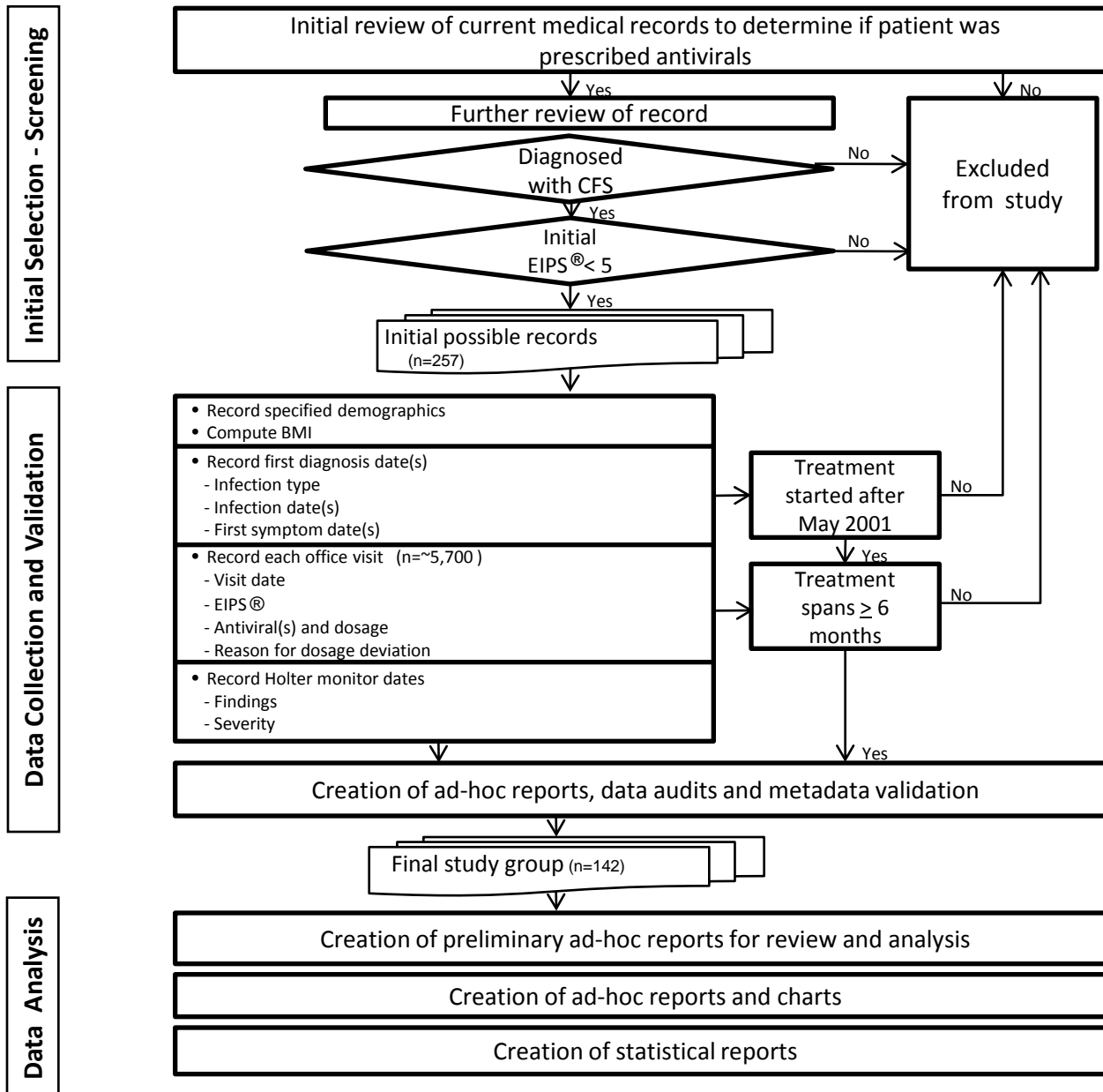
# Introduction

- I began my investigative career at the National Institute of Allergy and Infectious Diseases in 1955, a life changing experience!
- In 1988 I became suddenly ill
  - overwhelming fatigue
  - chest ache
  - 24 Hr. ECG suggested an acute myocardial infarction
  - heart was grossly dilated
  - diagnosed with acute dilated cardiomyopathy of unknown cause
- From 1988 through 1996, I was an invalid with life altering fatigue
- In 1996 I was the first patient treated by the Method we outline today

# Data Collection: Method

- 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.
- Today 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



# CFS Groups & Subsets: Identified Through Chart Review

## CFS Patient Criteria Requirements

- Herpesvirus elevated IgG serum titer(s)
- Treatment started after May 2001
- Initial EIPS<sup>®</sup> of  $\leq 5$
- Treatment duration was for  $> 6$  months

### Group A

Single/Multiple Herpesvirus

- EBV
- HCMV
- HHV6

### Group B

Group A plus co-infection(s)

- Lyme: Babesiosis, Anaplasmosis
- Adult Rheumatic Fever

# CFS Subsets: International Clinical Criteria for CFS, Specific Diagnostic Panel for Group A CFS Patients

- I. Elevated serum IgG antibody titers / single or multiple herpesvirus infection
  1. EBV, EA (47Kda recombinant peptide) and/or EBV, VCA IgM (p18 recombinant peptide)
  2. HCMV, AD 69 (fibroblast lysate) and/or
  3. HHV6 ( $\geq 160$ )
- II. Negative, Serum Antibody Titers
  1. Borrelia burgdorferi (ELISA and W. Blot, CDC antigens)
  2. Babesia microti
  3. Anaplasma phagocytophila
  4. ASO ( $< 400$ )
  5. Mycoplasma pneumoniae ( $> 2x$  normal)
- III. Cardiac Abnormalities, 24 Hr. ECG Holter monitor
- IV. EIPS<sup>®</sup>  $\leq 5$



# Energy Index Point Score<sup>®</sup> :

## 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   |

US copyright, Lerner, A.M. and Deeter, R. G. 1999  
Reference: In Vivo 2008:22; 799-802

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Many patients do not consider  
their most debilitating symptoms  
Other common symptoms

- Decreased energy of 50% or more
- Need to rest or nap daily
- Fever
- Chills and night sweats
- Palpitations
- Light-headedness
- Sore throat
- Painful lymph nodes
- Weakness
- Muscle aches
- Exercise intolerance
- ...

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As the Energy Index Point Score (EIPS) rises from 6 to 10, symptoms of syncope, chest pain, muscle aches, palpitations and the need to nap during the day lessen.

# Energy Index Point Score®: Validation (Method of Construct Validity)

- I.
    - a. 20 CFS patients, 17 F, 3 M,  
mean age of 41 years, EIPS = 3.6
    - b. 22 healthy adults, 17 F, 5 M,  
mean age 35 years, EIPS = 9.9
  - c. Effect Size: EIPS, 0.25 small, 0.50 medium, >0.8 large
- p = 0.001
- II. Simultaneous evaluations, EIPS and Fatigue Severity  
Score, 55 consecutive patients correlation 0.67, p = 0.0001

**The Energy Index Point Score is a valid  
metric to assess the CFS patient.**

# Energy Index Point Score<sup>®</sup> : International Use

- The EIPS<sup>®</sup>:
  - is a quick, easy, dependable, accurate and repeatable metric
  - provides users with a validated understanding of one's health
  - is currently in use by other physicians and is posted on other physician/medical web sites
  - has been translated into other languages

# Schedule: Physician Treatment

- Patient Visits Every 4-6 weeks
- EIPS<sup>®</sup> – Collaboration (patient & physician)
- Physical examination
- Syncope, tachycardia at rest
- 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

# Schedule: 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

# Demographics: 106 Group A CFS Patients

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

<sup>1</sup> t Test (2-tail) to determine differences between men and women

<sup>2</sup> Paired t Test (2-tail) to determine difference between baseline and last "EIPS®"

\* Last "EIPS®" minus first "EIPS®"



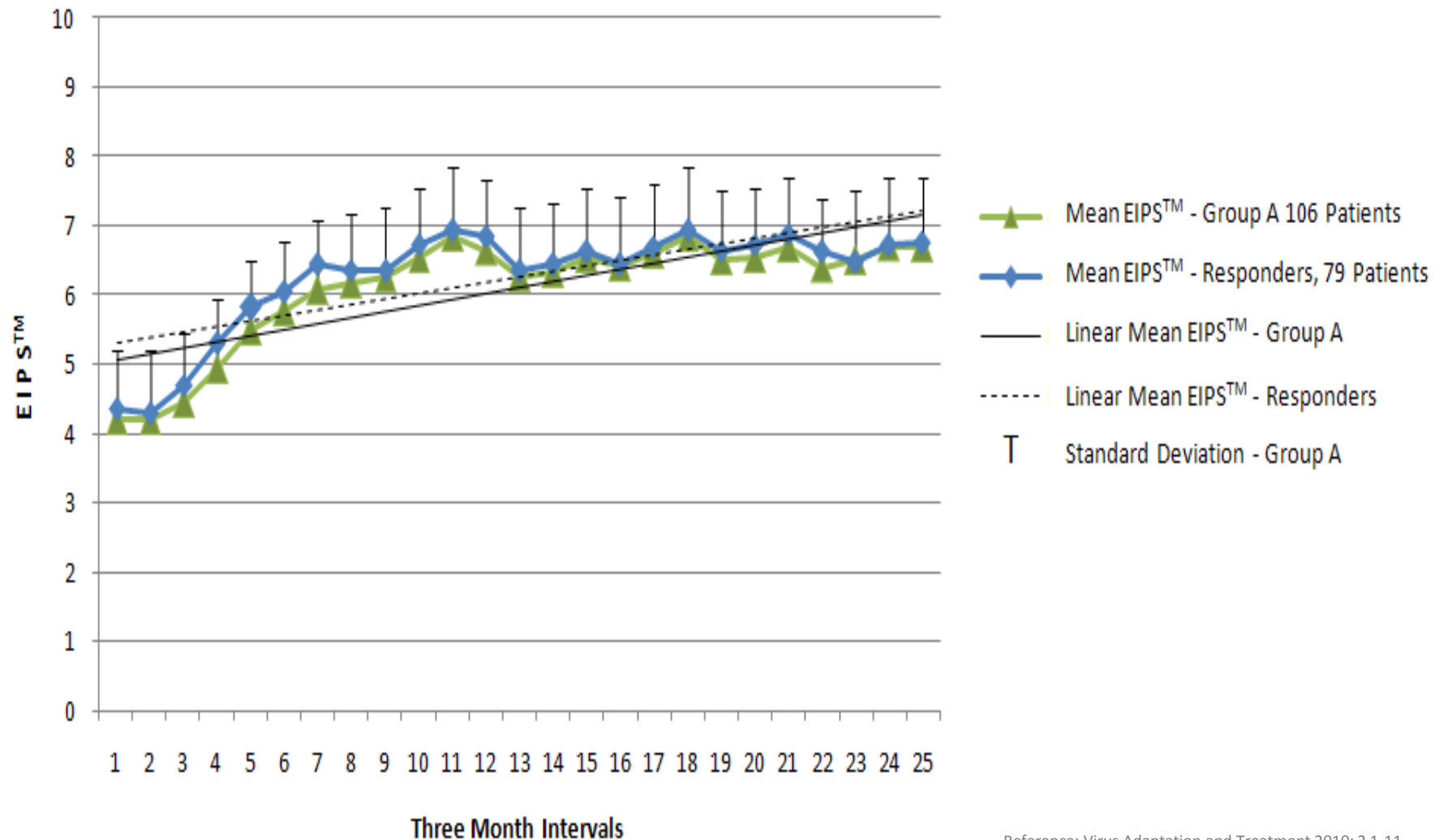
# Results: Mean EIPS® at Three-month Intervals for 106 Group A CFS Patients Including 79 (74.5%) Group A “Responders”

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	<p>Increase of Mean EIPS from 4.21 to a high of 6.70.</p> <p>From only 4-6 hrs out of bed to a full time job!</p>	0		4.36	0.80
1	98	4.19		1		4.29	0.93
2	104	4.44		2		4.70	1.19
3	103	4.94		3		5.30	1.47
4	96	5.49		4		5.84	1.40
5	84	5.77		5		6.03	1.37
6	78	6.06		6		6.44	1.24
7	66	6.17		7		6.37	1.25
8	59	6.25		8		6.35	1.20
9	51	6.55		9		6.71	0.82
10	47	6.83		10		6.94	0.98
11	46	6.65		11		6.84	0.97
12	40	6.26		12		6.35	1.33
13	38	6.32		13		6.44	1.39
14	38	6.54		14		6.63	1.32
15	33	6.42		15		6.45	1.18
16	30	6.59		16		6.70	1.03
17	28	6.83		17		6.94	1.10
18	27	6.52		18		6.64	1.34
19	22	6.55		19		6.74	1.31
20	18	6.69		20		6.89	1.74
21	14	6.40		21		6.64	1.40
22	13	6.51		22		6.47	0.92
23	13	6.70		23		6.72	0.92
24	6	6.70		24		6.88	1.49

# Results: Improvement in EIPS<sup>®</sup> 106 Group A CFS Patients after Antiviral Therapy



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

# Results: Single and Multiple (2-3) Herpesvirus CFS Subsets Among 106 Group A Patients

<u>Single Herpesvirus CFS</u>	Females	Males	Totals
Epstein-Barr virus (EBV)	20 patients	10 patients	30 patients (28.3%)
Cytomegalovirus (HCMV)	8 patients	5 patients	13 patients (12.3%)
Human Herpesvirus 6 (HHV6)	<u>2 patients</u>	<u>0</u>	<u>2 patients (1.9%)</u>
<b>Total</b>	<b>30 patients</b>	<b>15 patients</b>	<b>45 patients (42.5%)</b>

Pearson Chi Square p=0.562

<u>Multiple Herpesvirus CFS</u>	Females	Males	Totals
EBV/HCMV	24 patients	6 patients	30 patients (28.3%)
EBV/HCMV/HHV6	7 patients	5 patients	12 patients (11.3%)
EBV/HHV6	11 patients	3 patients	14 patients (13.2%)
HCMV/HHV6	<u>5 patients</u>	<u>0</u>	<u>5 patients (4.7%)</u>
<b>Total</b>	<b>47 patients</b>	<b>14 patients</b>	<b>61 patients (57.5%)</b>

Pearson Chi Square p=0.258

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

Presented by A. Martin Lerner, MD., M.A.A.C.P., HHS, CFS Advisory Committee Science Day - Washington DC, October 12, 2010

# Results: Demographics of 106 Group A Herpesvirus CFS Patients, 2001-2007, “Responders and Non-responders”

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

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<sup>1</sup> Fisher’s Exact Test (2-Tail)

<sup>2</sup> t Test (2-Tail)

<sup>3</sup> Multivariate analysis of variance with repeated measures

# Results: 142 CFS Patient Systematic Review

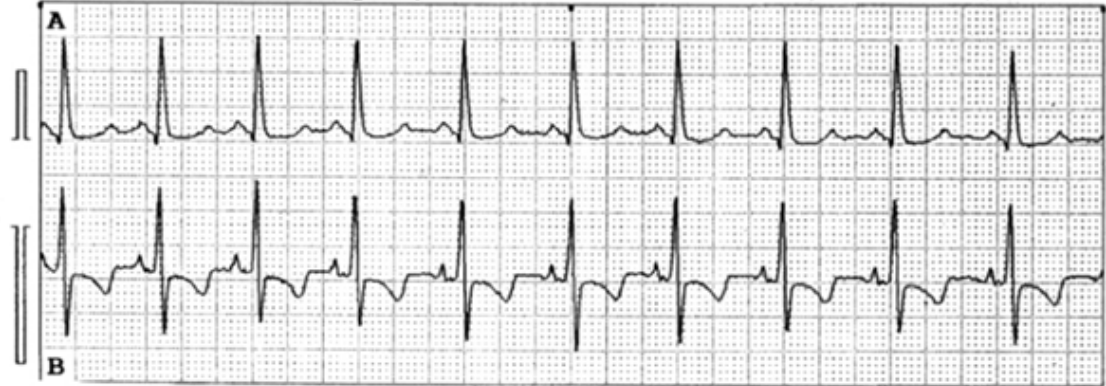
- EIPS values increased significantly
- Cardiac, immunologic, and neurocognitive abnormalities improved and/or disappeared
- 106 CFS Patients (Group A EBV, HCMV, HHV6 in single or multiple infection with no co-infections)
  - Treated with subset-directed antiviral nucleosides, valacyclovir and valganciclovir 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

# Results: Sequential Holter Monitoring of a 31 year Old Woman with CFS

Before Valacyclovir Therapy

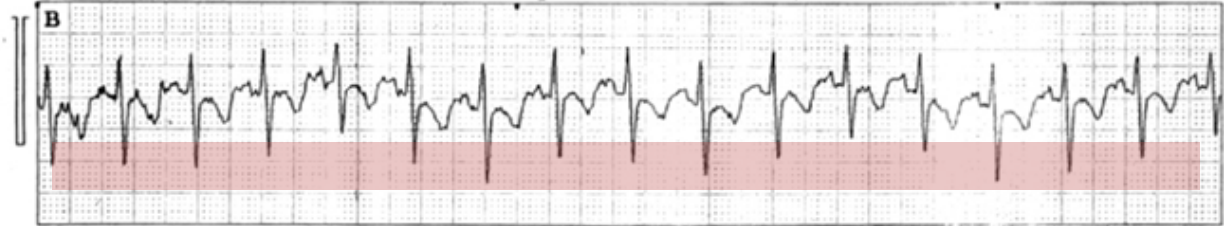
May 11, 1996

ECG 23 1:40:22 PM SV Rhythm, Rate 100-150



January 7, 1997

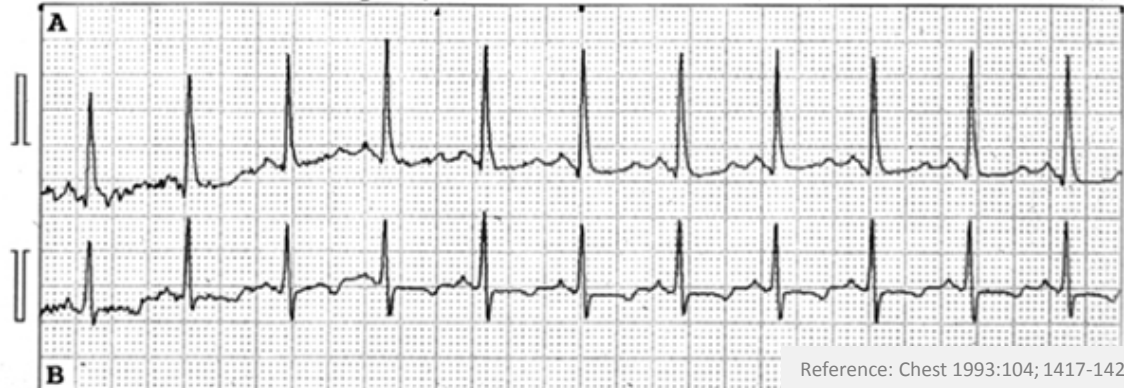
ECG 3 7:57:26 PM Maximum ST Depression (Channel B)



After Valacyclovir Therapy

October 17, 1997

ECG 51 5:11:21 AM SV Rhythm, Rate 100-150



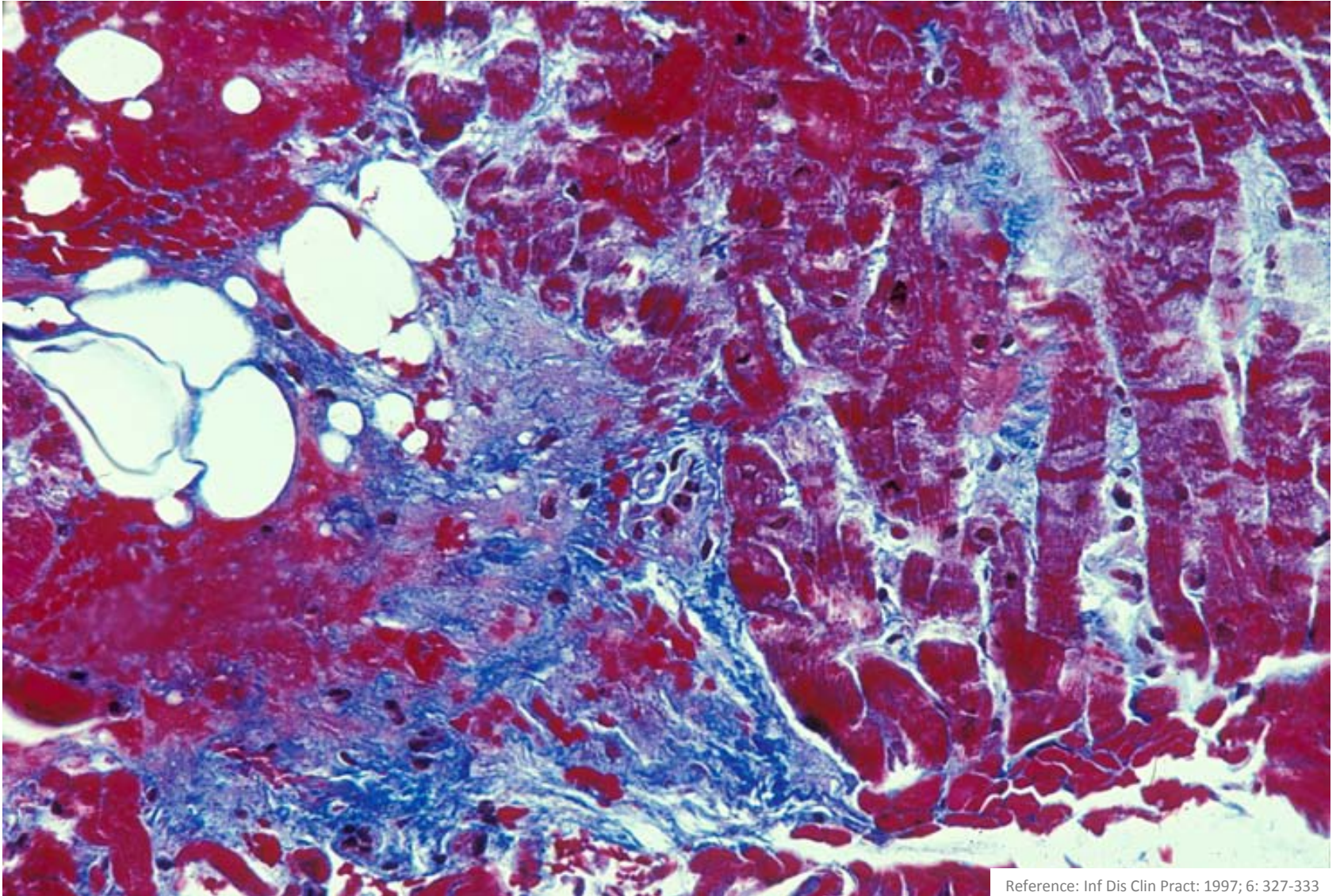
Reference: Chest 1993;104:1417-1420

# Results: 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



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

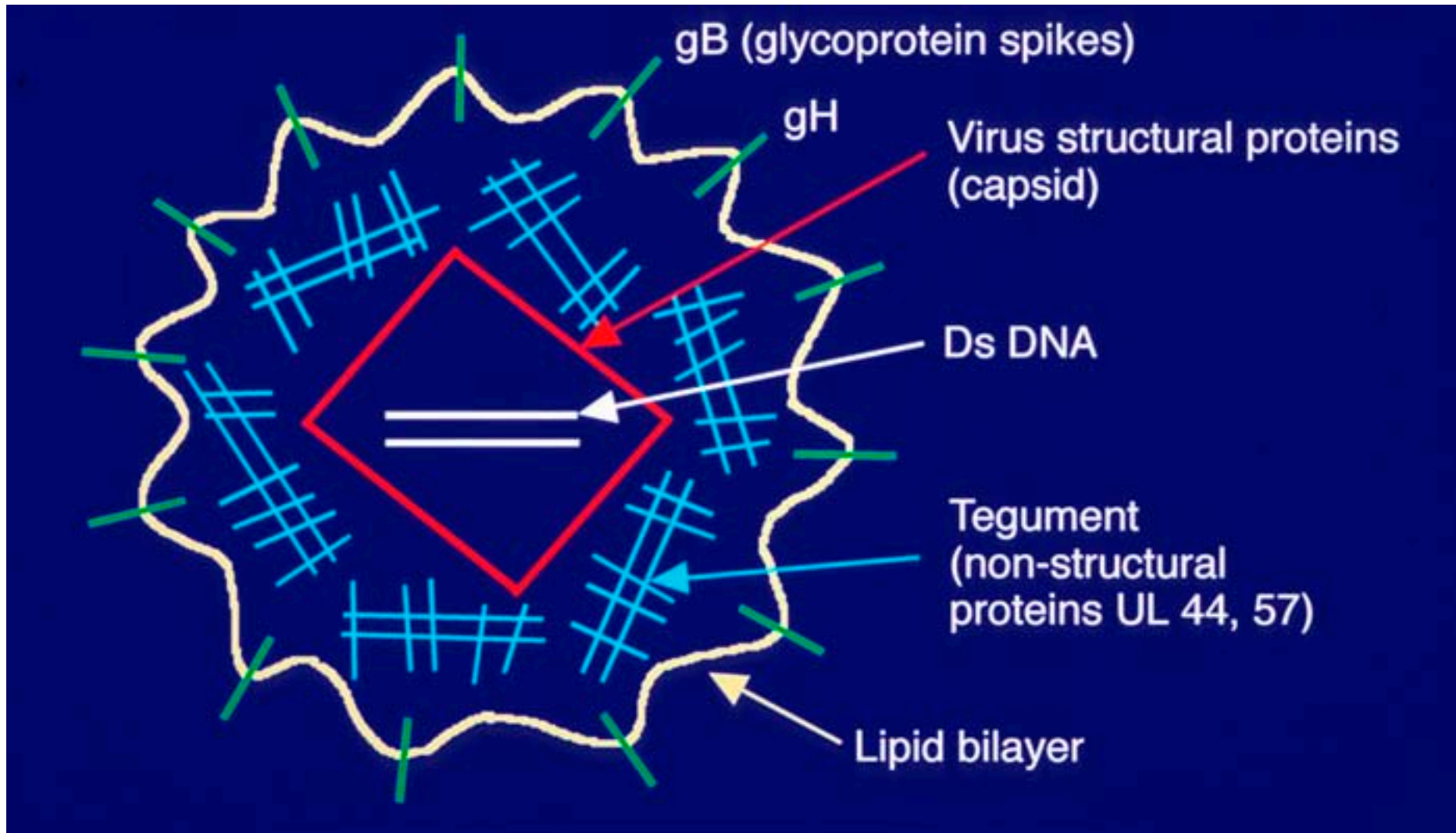


Reference: Inf Dis Clin Pract: 1997; 6: 327-333



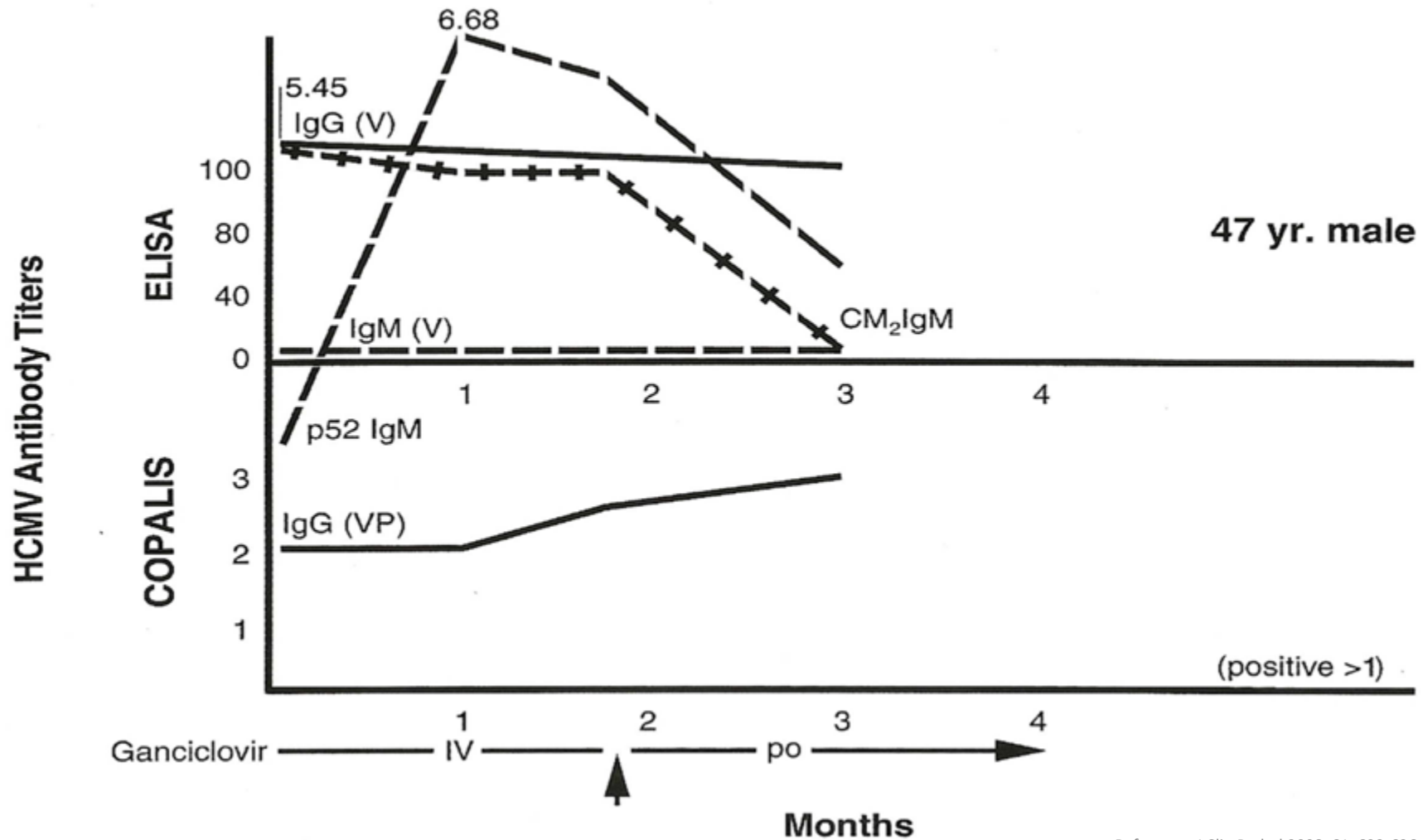
# The Science:

## Herpesvirus Complete Virion



# The Science: Single HCMV CFS

## Non-Permissive Multiplication



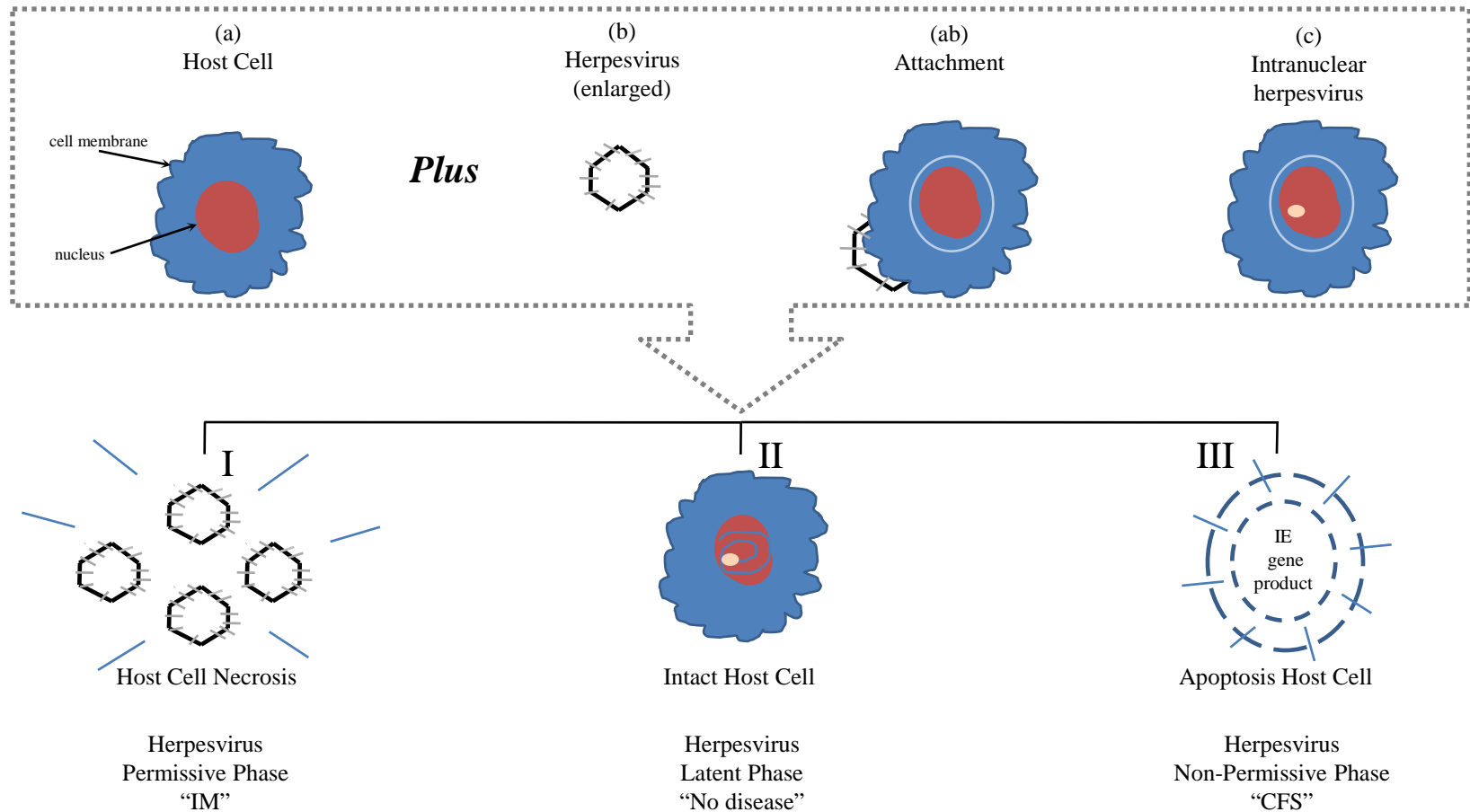
Reference: J Clin Pathol 2008; 61; 623-626

# The Science: Comparative Herpesvirus Permissive and Non-Permissive Replication

	Result	Replication	
		Permissive	Non-Permissive
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

Reference: Submitted for publication

# The Science: 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, "CFS."

# The Science: EBV, Immediate Early Gene Zta (BZLF1 and EB1) Induces Apoptosis

1. Binds to AP-1 sites altering host cell signaling
2. Induces IL-6, IL-10, TGF $\beta$ , tyrosine kinase TKT, matrix metalloproteinases (MMP1 and MMP-9) c-Fos, early growth response (Egr-1)

# The Science: EBV, Immediate Early Gene Zta (BZLF1 and EB1) Induces Apoptosis

Continued

Zta is taken up by both infected and non-infected cells inhibiting certain arms of the immune process e.g. IL-10, decreasing macrophage and NK cell functions and T-cell mediated cytotoxic responses, MHC class 1 molecules and immune presentations of lytic antigens, major tumor necrosis factor alpha (TNF-R1) minimizing response to TNF receptor mediated apoptosis signaling interferons A, B, and  $\gamma$ . Zta mediates these signaling events without EBV gene progressions to the lytic cascade.

Reference: Submitted for publication

# 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 nonpermissive 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 treatments is successful!

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



# Thank You!

A. Martin Lerner, MD  
Birmingham, Michigan

<http://www.treatmentcenterforcfs.com/>