Multiple Systemic Infections in Chronic Illnesses and the Use of Membrane Lipid Replacement to Restore Mitochondrial Function and Reduce Symptoms

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Disclosures and Documents

- Prof. Emeritus of Pathology & Laboratory Medicine
- President, Founder & Chief Scientific Officer, Institute for Molecular Medicine in California
- Consultant to: Allergy Research Group, Inc., Nutritional Therapeutics, Inc., Researched Nutritionals, Inc., Naturally Plus Japan & USA
- Publications: Download as PDF docs at Research Gate (Berlin), ResearchGate.net or Open Access Journal Sources (550 out of 650)

Lecture Outline

- Multiple Systemic Infections (MSID) are commonly found in chronic diseases and result in damage to mitochondrial and other cellular membrane systems
- Membrane Lipid Replacement Therapy (MLR) with protected glycerolphospholipids replaces damaged membrane phospholipids and restores function
- Membrane Lipid Replacement Therapy (MLR) reduces fatigue and enhances mitochondrial function by restoring Inner membrane trans-membrane potential and increasing production of ATP
- Membrane Lipid Replacement Therapy (MLR) reduces pain and other symptoms in Lyme, Fibromyalgia and other illnesses
- Membrane Lipid Replacement improves blood biomarkers associated with chronic diseases

Multiple Systemic Infections in Various Diseases

- Neurodegenerative Diseases (ALS, PD, AD, MS)
- Neurobehavioral Diseases (ASD, ADD, ADHD)
- Fatiguing Illnesses (CFS/ME, FM, GWI)
- Autoimmune Diseases (MS, SLE, IBS)
- Rheumatic Diseases (RA, SD, OA, SS)
- Chronic Infectious Diseases (Lyme, Hep, CIM)
- Immunosuppressive Diseases (HIV-AIDS, MDS, NHL)

British Journal of Medical Practitioners 2009; Vol. 2, No. 4, pp. 20-28.

Role of Chronic Bacterial and Viral Infections in Neurodegenerative, Neurobehavioral, Psychiatric, Autoimmune and Fatiguing Illnesses: Part 1

Garth L. Nicolson[1*] and Jörg Haier[2]

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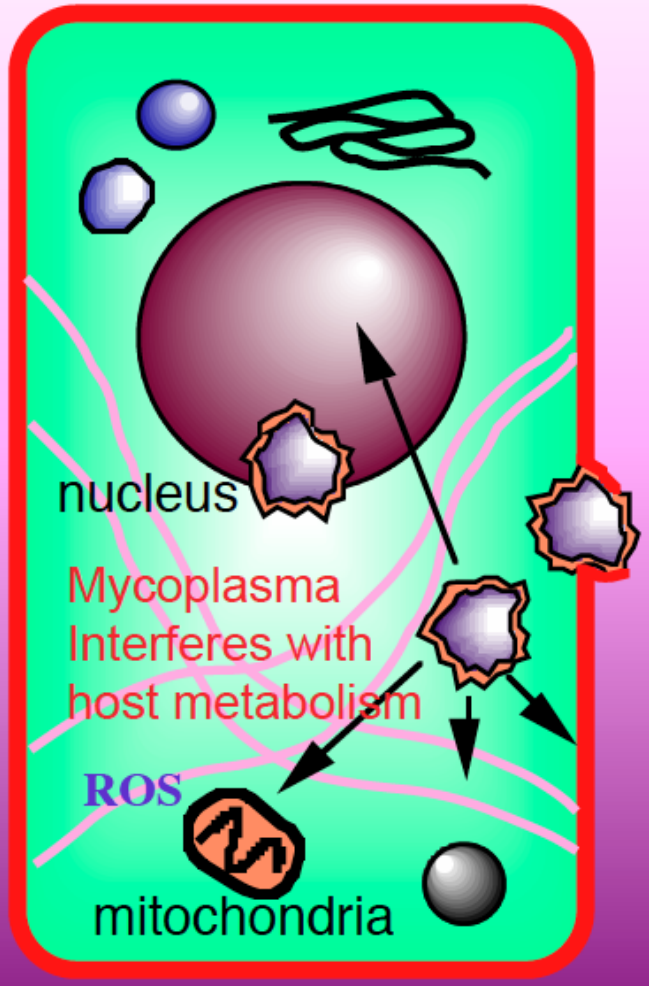
Abstract

Chronically ill patients with neurodegenerative, neurobehavioral and psychiatric diseases commonly have systemic and central nervous system bacterial and viral infections. In addition, other chronic illnesses where neurological manifestations are routinely found, such as fatiguing and autoimmune diseases, Lyme disease and Gulf War illnesses, also show systemic bacterial and viral infections that could be important in disease inception, progression or increasing the types/severities of signs/symptoms. Evidence of *Mycoplasma* species, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, human herpesvirus-1, -6 and -7 and other bacterial and viral infections revealed high infection rates in the above illnesses that were not found in controls. Although the specific roles of chronic infections in various diseases and their pathogeneses have not been carefully determined, the data suggest that chronic bacterial and/or viral infections are common features of progressive chronic diseases.

Multiple Systemic Infections in Chronic Diseases

- Chronic infections (viral, bacterial, fungal) could be the **cause**, along with genetic and environmental factors, of the disease
- Chronic infections (viral, bacterial, fungal) could be a **co-factor**, along with chemicals, toxins, heavy metals, etc., in the disease
- Chronic infections (viral, bacterial, fungal) could be **opportunistic**, and occur after immune suppression
- Chronic infections (viral, bacterial, fungal) could cause a **co-morbid** condition in the disease

Cell



Intracellular chronic bacterial infections
Cause damage to cellular structures

Example:
Pathogenic Mycoplasmas

Mycoplasma host mimick antigens

Host cell antigens

Mycoplasma super antigens

1. Release of toxins
2. Competes for metabolites
3. Alters cellular structures
4. Releases host antigens
5. Stimulates ROS/RNS

Prof. Garth L. Nicolson
The Institute for Molecular Medicine

Laboratory Medicine 2008; 39(5): 291-299.
Official Journal of the American Society of Clinical Pathology

Review

Chronic Bacterial and Viral Infections in Neurodegenerative and Neurobehavioral Diseases

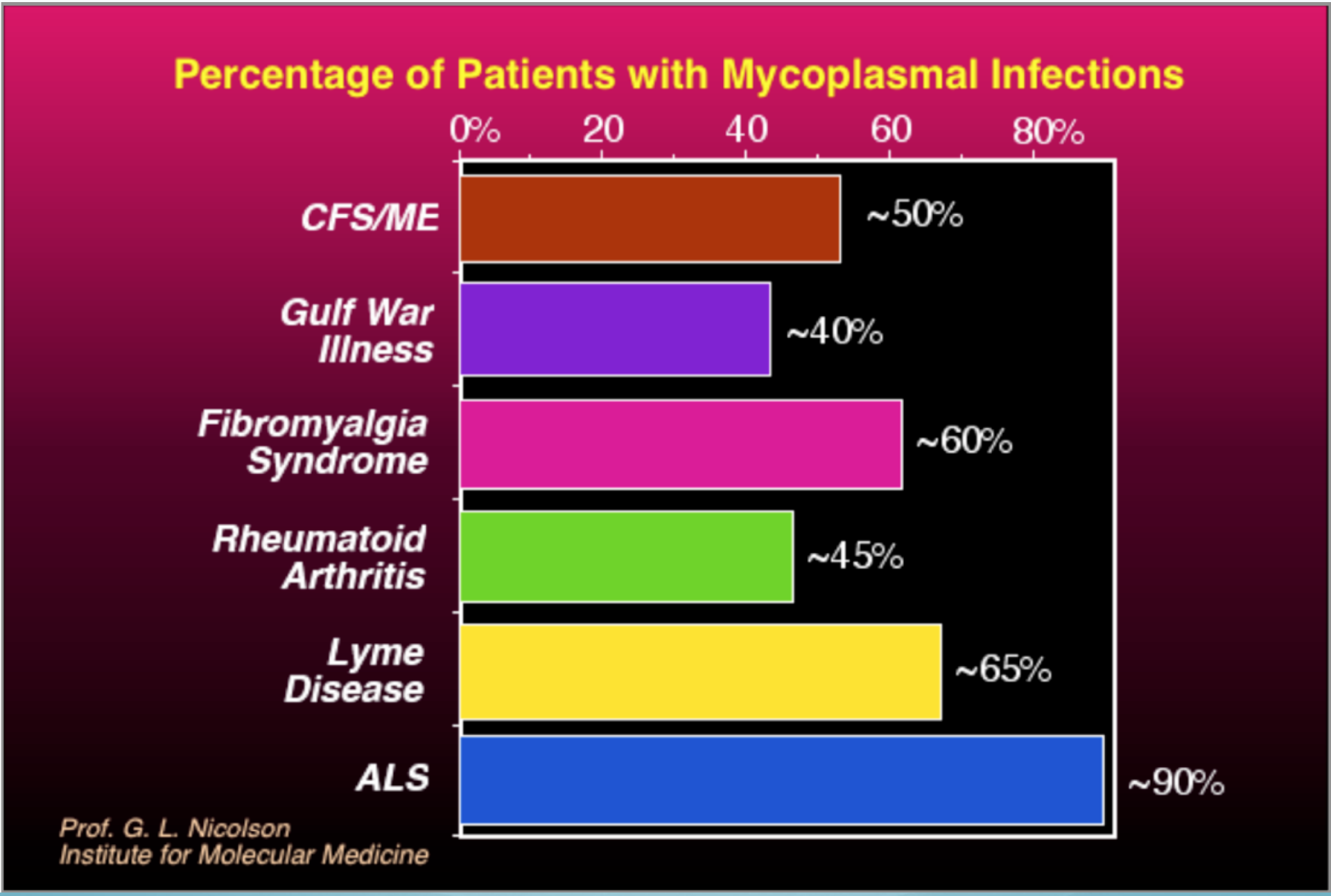
Garth L. Nicolson, PhD
(Department of Molecular Pathology, The Institute for Molecular Medicine, Huntington Beach, CA)

DOI: 10.1309/96M3BWYP42L11BFU

Abstract

Often, patients with neurodegenerative or neurobehavioral diseases have chronic, neuropathic infections that could be important in disease inception, disease progression, or increasing the types or severities of signs and symptoms. Although controversial, the majority of patients with various neurodegenerative or neurobehavioral conditions, such as amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and autistic spectrum disorders, show evidence of central nervous system or systemic bacterial and viral infections. For example, using serology or polymerase chain reaction evidence of *Chlamydia pneumoniae, Borrelia burgdorferi, Mycoplasma* species, human herpesvirus-1 and -6, and other bacterial and viral infections revealed high infection rates that were not found in control subjects. Although chronic infections were not found in some studies, and the specific role of chronic infections in neurological disease pathogenesis has not been determined or is inconclusive, the data suggest that chronic bacterial or viral infections could be common features of progressive neurodegenerative and neurobehavioral diseases.

Some Examples of Illnesses with Chronic Mycoplasmal Infections



The presence of multiple chronic bacterial and viral infections is related to severities of 120 signs and symptoms in CFS/ME and FM patients

Nicolson et al. APMIS 2003; 111: 557-566.

APMIS 111: 557–66, 2003
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APMIS
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Multiple co-infections (*Mycoplasma, Chlamydia*, human herpes virus-6) in blood of chronic fatigue syndrome patients: association with signs and symptoms

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[3]Department of General Surgery, University Hospital, Muenster, Germany

Nicolson GL, Gan R, Haier J. Multiple co-infections (*Mycoplasma, Chlamydia*, human herpes virus-6) in blood of chronic fatigue syndrome patients: association with signs and symptoms. APMIS 2003;111:557–66.

Previously we and others found that a majority of chronic fatigue syndrome (CFS) patients showed evidence of systemic mycoplasmal infections, and their blood tested positive using a polymerase chain reaction assay for at least one of the four following *Mycoplasma* species: *M. fermentans*, *M. hominis*, *M. pneumoniae* or *M. penetrans*. Consistent with previous results, patients in the current study (n=200) showed a high prevalence (overall 52%) of mycoplasmal infections. Using forensic polymerase chain reaction we also examined whether these same patients showed evidence of infections with *Chlamydia pneumoniae* (overall 7.5% positive) and/or active human herpes virus-6 (HHV-6, overall 30.5% positive). Since the presence of one or more infections may predispose patients to other infections, we examined the prevalence of *C. pneumoniae* and HHV-6 active infections in mycoplasma-positive and -negative patients. Unexpectedly, we found that the incidence of *C. pneumoniae* or HHV-6 was similar in *Mycoplasma*-positive and -negative patients, and the converse was also found in active HHV-6-positive and -negative patients. Control subjects (n=100) had low rates of mycoplasmal (6%), active HHV-6 (9%) or chlamydial (1%) infections, and there were no co-infections in control subjects. Differences in bacterial and/or viral infections in CFS patients compared to control subjects were significant. Severity and incidence of patients' signs and symptoms were compared within the above groups. Although there was a tendency for patients with multiple infections to have more severe signs and symptoms ($p<0.01$), the only significant differences found were in the incidence and severity of certain signs and symptoms in patients with multiple co-infections of any type compared to the other groups ($p<0.01$). There was no correlation between the type of co-infection and severity of signs and symptoms. The results indicate that a large subset of CFS patients show evidence of bacterial and/or viral infection(s), and these infections may contribute to the severity of signs and symptoms found in these patients.

Key words: Chronic fatigue syndrome; infection; *Mycoplasma*; human herpes virus-6; *Chlamydia*.

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"Old" versus "New" Thinking in Explaning Chronic Illnesses

Infections	*Genetics*	*Immunity*	*Environ. Toxins*		*Result*
Old Thinking: Only Infection A causes Disease or Syndrome A					
Infection A →					Disease A
New Thinking: Multiple infections, genetic/immune abnormalities, toxic exposures, etc. can result in Syndrome B or co-morbid conditions					
Infection B	Gene 1	Immune a	Toxin 1	Metal x	
Infection C	Gene 2	Immune b	Toxin 2	Metal y	Syndrome B
Infection D	Gene 3	Immune c	Toxin 3	Metal z	

Autism Spectrum Disorders (ASD)

- Pervasive brain developmental disorders causing severe impairment in thinking, feeling, communication
- Repetitive behavior and and inability to relate to others
- First seen in early childhood (Autism, Asperger's syndrome, others)
- Some genetic and environmental toxic links (infections, chemicals, heavy metals, biotoxins)

Autism Spectrum Disorders (ASD)

Some Children Become Autistic After:

- Multiple Childhood Vaccinations
- Acute Childhood Infections
- Chemical Exposures
- Heavy Metal Exposures
- Combinations of the Above

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Journal of Neuroscience Research 85:1143–1148 (2007)

Evidence for Mycoplasma ssp., Chlamydia pneunomiae, and Human Herpes Virus-6 Coinfections in the Blood of Patients With Autistic Spectrum Disorders

Garth L. Nicolson,[1]* Robert Gan,[1] Nancy L. Nicolson,[1] and Joerg Haier[1,2]

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[2]Department of Surgery, University Hospital, Munster, Germany

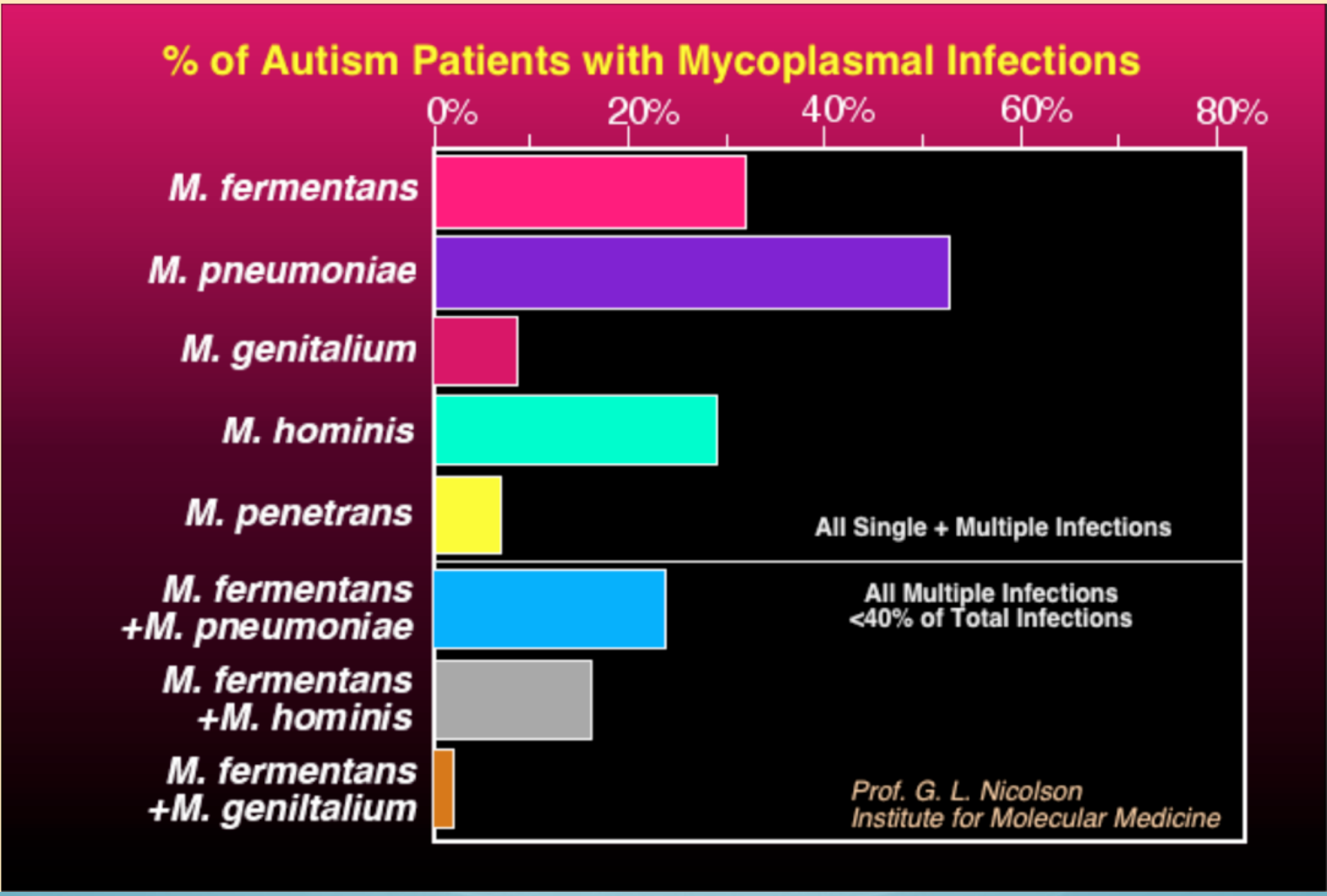
We examined the blood of 48 patients from central and southern California diagnosed with autistic spectrum disorders (ASD) by using forensic polymerase chain reaction and found that a large subset (28/48 or 58.3%) of patients showed evidence of *Mycoplasma* spp. infections compared with two of 45 (4.7%) age-matched control subjects (odds ratio = 13.8, $P < 0.001$). Because ASD patients have a high prevalence of one or more *Mycoplasma* spp. and sometimes show evidence of infections with *Chlamydia pneumoniae*, we examined ASD patients for other infections. Also, the presence of one or more systemic infections may predispose ASD patients to other infections, so we examined the preva-

predictable ways (Berney, 2000). Autism and related disorders have been recently placed into a multidisorder category called autistic spectrum disorders (ASD), which includes autism, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), and other disorders (Keen and Ward, 2004).

The criteria for diagnosis of ASD are, in general terms, the presence of a triad of impairments in social interaction, communication, and imagination (Wing et al., 2002). These signs and symptoms are thought to be due to abnormalities in brain function or structure and are thought to have a genetic basis (Folstein and Rosen-Sheidley, 2001; Veenstra-Vanderweele et al.,

Northern California ASD Study

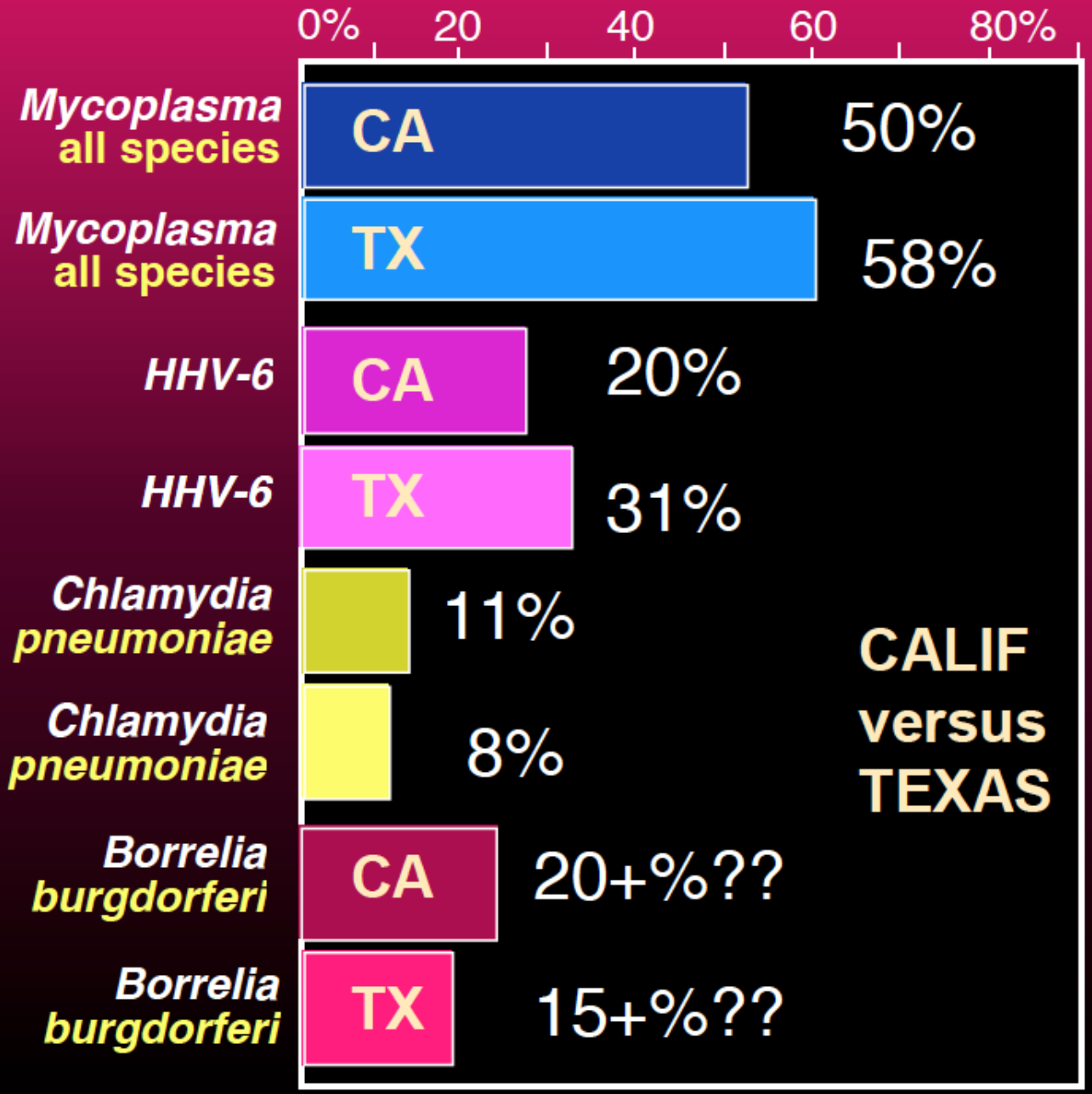
- 68 ASD patients (58% Mycoplasma species-positive, various species (M. fermentans, M. hominis, M. pneumoniae, etc.) Odds Ratio = 13.8 ($p<0.0001$)
- 68 ASD patients (8.3% Chlamydia pn.-positive) Odds Ratio = 5.6 ($p<0.001$)
- 68 ASD patients (29.2% HHV6-positive) Odds Ratio = 4.5 ($p<0.001$)
- 120 Healthy family members (6.5% Mycoplasma species-positive, 2.1% Chlamydia pn.-positive, 8.1% HHV6-positive)
- Multiple Chronic Infections Odds Ratio = 16.5 ($p<0.001$)


% of Autism Patients with Mycoplasmal Infections
0%
20%
40%
60%
80%
M. fermentans
M. pneumoniae
M. genitalium
M. hominis
M. penetrans
All Single + Multiple Infections
M. fermentans +M. pneumoniae
M. fermentans +M. hominis
M. fermentans +M. geniltalium
All Multiple Infections <40% of Total Infections
Prof. G. L. Nicolson
Institute for Molecular Medicine

ASD Chronic Infections

- Multiple Chronic Infections found at high frequency in ASD patients but only in low frequency in non-ASD children or in Adults in same family.
- In some of these ASD patients with chronic infections other exposures were often present (Heavy Metals) or presumed (Chemicals)
- Different locations revealed similar results (comparison of California with Texas ASD patients)

Percent ASD Patients with Various Microbial Species



Not all Pts had Multiple Species

ASD Chronic Infections

- Mycoplasma species (est. 40-65%).
- Chlamydia pn. (est. 5-10%)
- HHV6 (est. 15-30%)
- Borrelia species (est. 15-35%)
- PAN/PANDAS (est. 10-15%)
- CMV (est. 5-8%)
- Fungal (est. 10-15%)
- Others??

Source: R. Bransfield & G. Nicolson publications

10

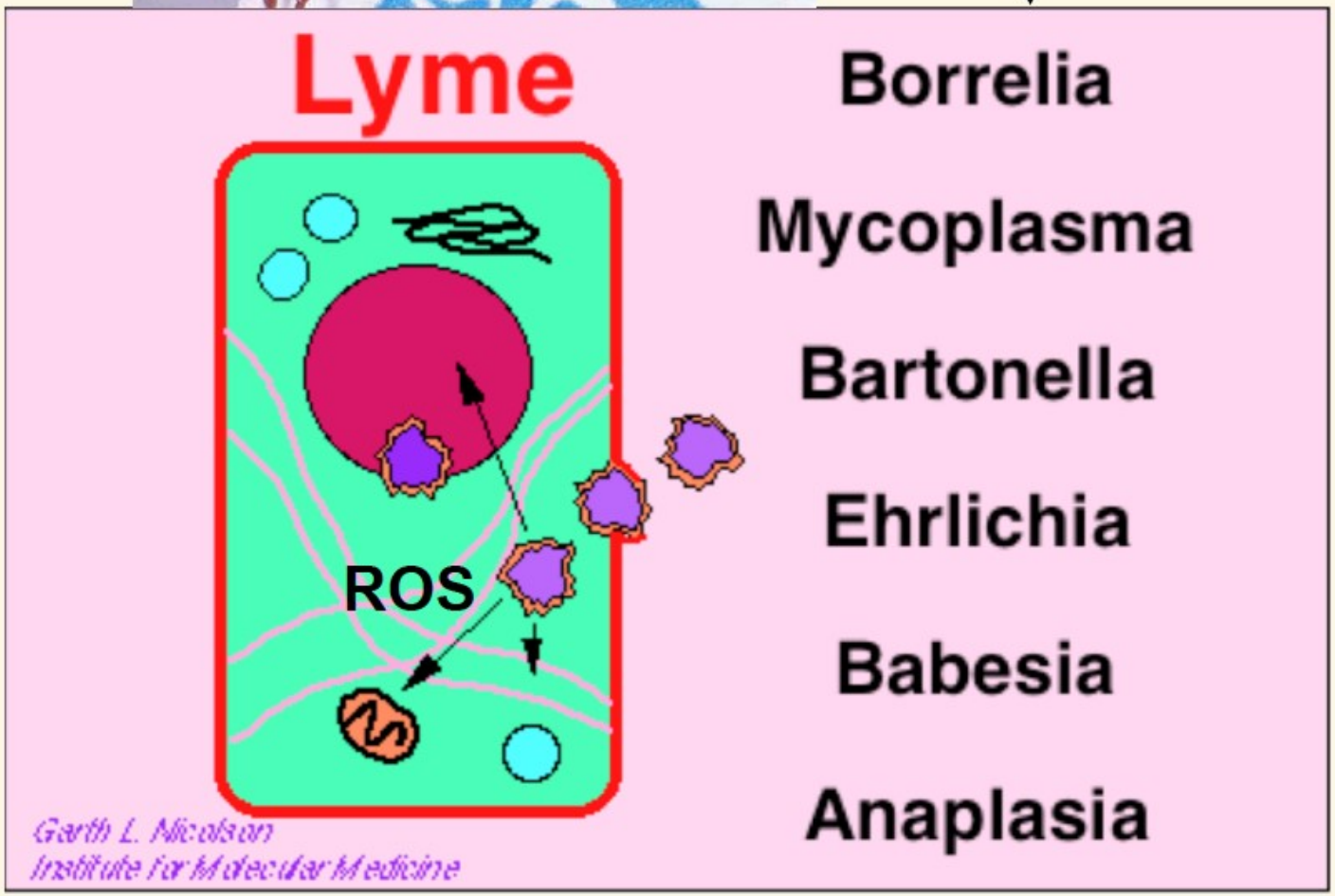
Lyme Disease and Tick-Borne Infections*

Causes and Physical and Neuropsychological Effects in Children

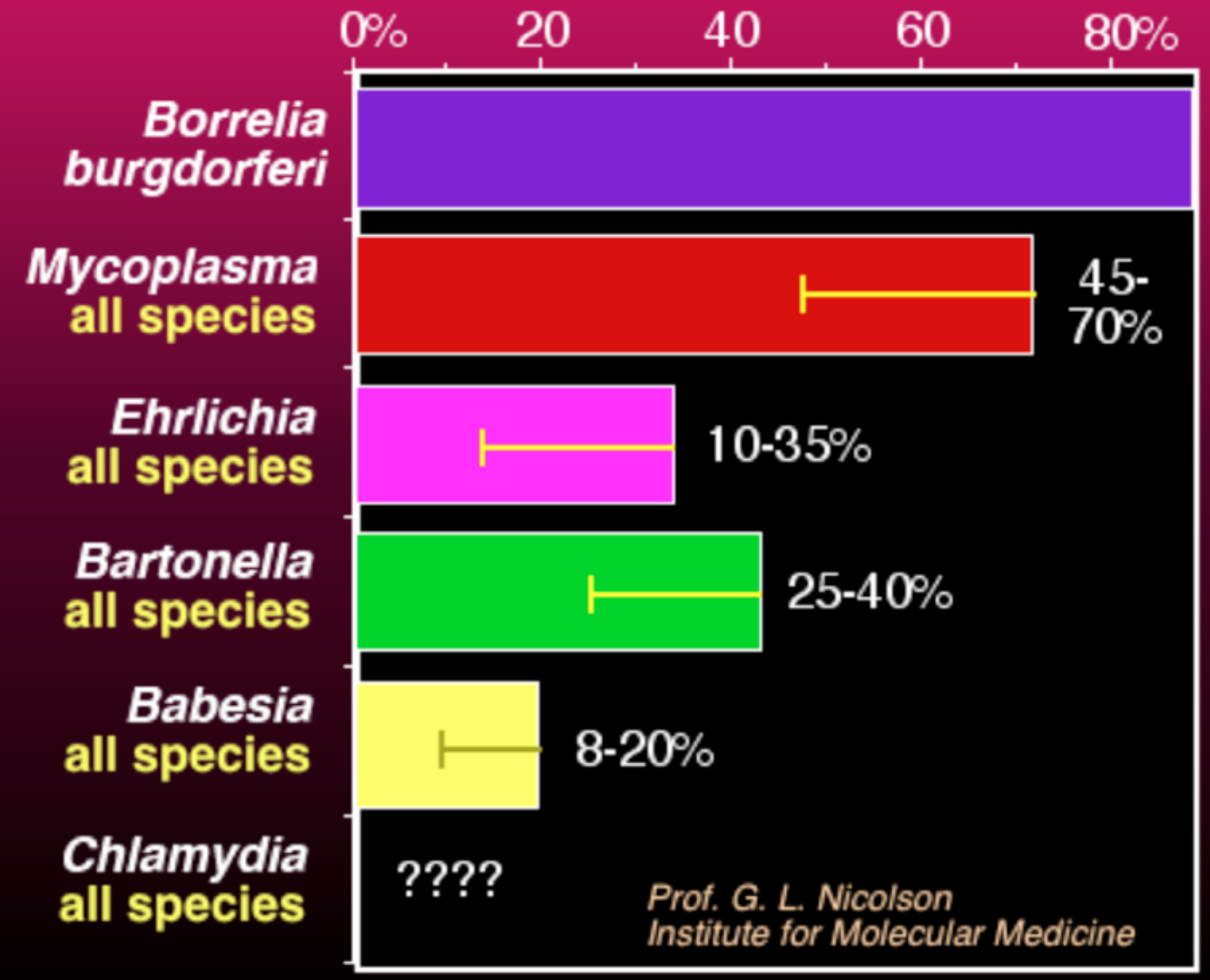
Ron Hamlen and Deborah S. Kliman

MSID-Lyme

Tick Bite



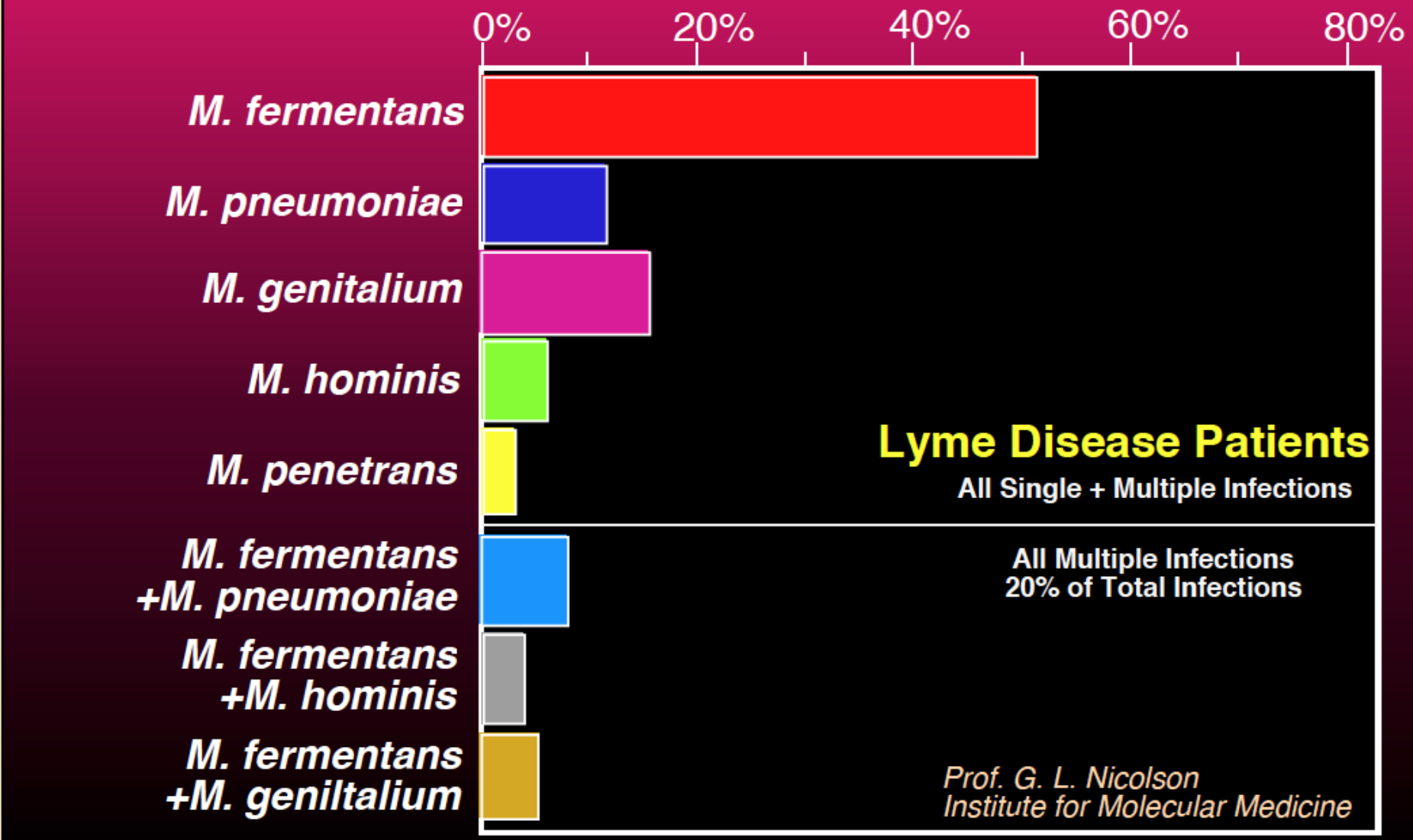
Some Lyme Patients Contain Various Microbial Species



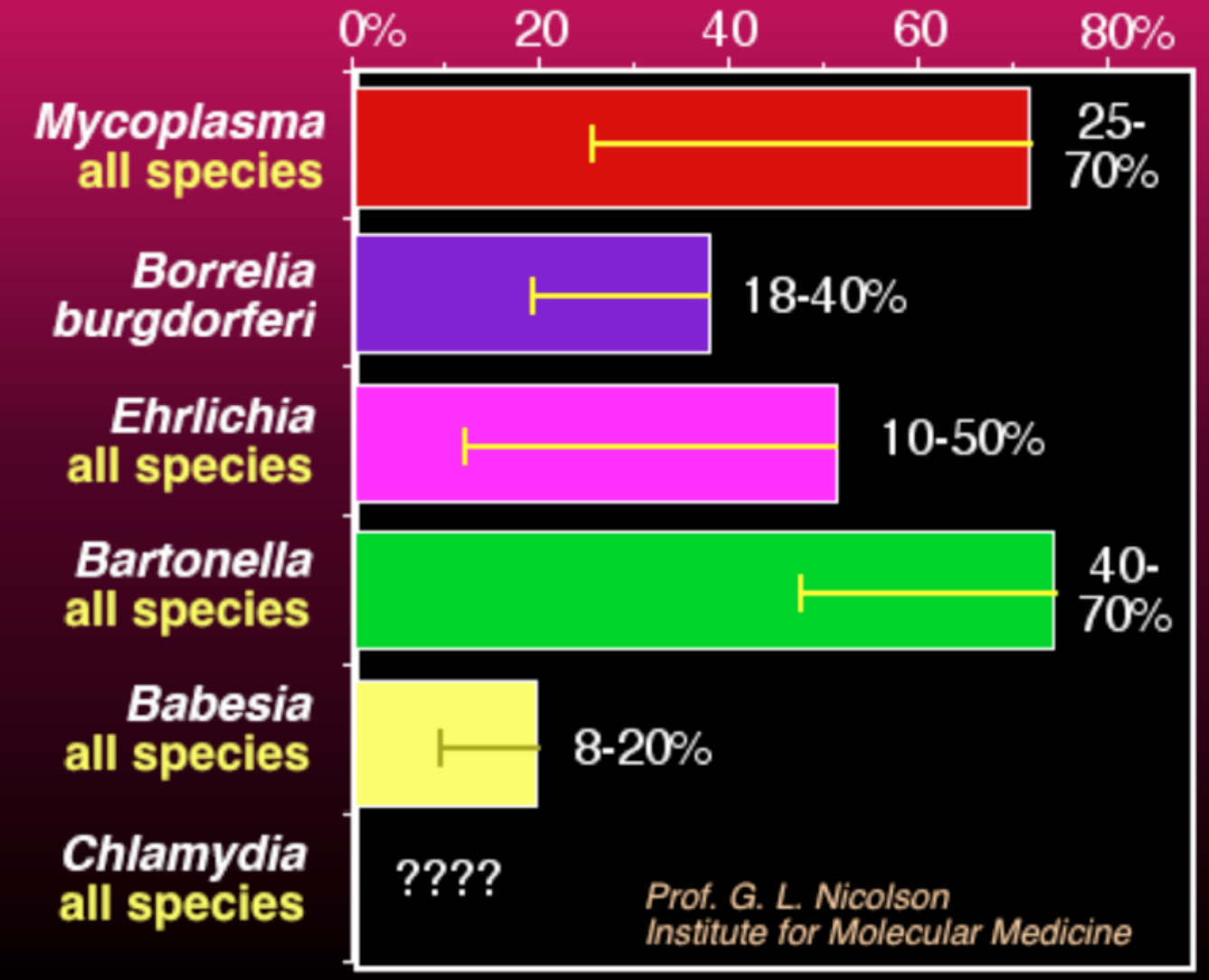
Range to Highest Incidence Obtained

Not all Pts had Multiple Species

Percent of Lyme Disease Patients with Mycoplasmal Infections



Some Ticks Contain Various Microbial Species (Extreme Cases)



Range to Highest Incidence Obtained

Not all Ticks had Multiple Species

Journal of Chronic Fatigue Syndrome 2008; 14(4): 5-17.

Chronic Fatigue Syndrome Patients Subsequently Diagnosed with Lyme Disease *Borrelia burgdorferi*: Evidence for *Mycoplasma* species Co-Infections

Garth L. Nicolson, PhD, Nancy L. Nicolson, PhD, Joerg Haier, MD, PhD

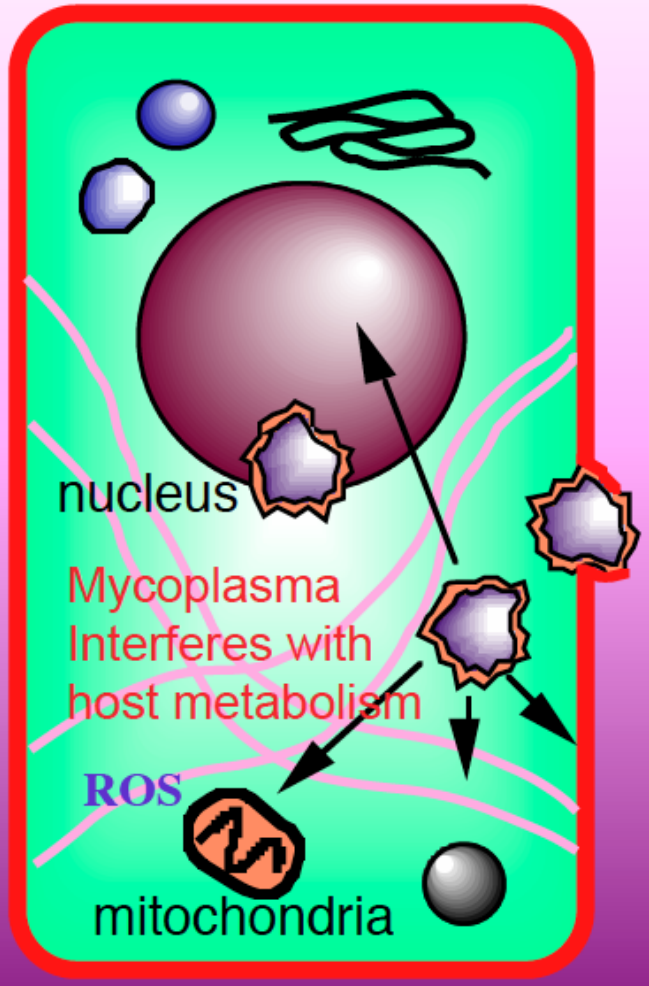
The Institute for Molecular Medicine, Huntington Beach, California, USA, Department of Surgery, University Hospital, Munster, Germany

ABSTRACT. *Objective:* We examined the blood of 48 North American Chronic Fatigue Syndrome (CFS) patients subsequently diagnosed with Lyme Disease *Borrelia burgdorferi* and compared these to 50 North American CFS patients without evidence of *Borrelia burgdorferi* infections for presence of *Mycoplasma spp.* co-infections using forensic polymerase chain reaction. *Results:* We found that 68.75% of CFS/Lyme patients show evidence of mycoplasma co-infections (Odds Ratio=41.8, Confidence Limits=11.26-155.16, $p<0.001$) compared to controls, whereas 50% of CFS patients without a diagnosis of Lyme Disease *Borrelia burgdorferi* show mycoplasma co-infections (OR=19.0, CL=5.25-68.78, $p<0.001$ compared to controls). Since CFS patients without a diagnosis of Lyme Disease have a high prevalence of one of four *Mycoplasma* species and a majority show evidence of multiple infections, we examined CFS/Lyme patients' blood for various *Mycoplasma* species. We found that CFS patients with Lyme Disease *Borrelia burgdorferi* mostly had single species mycoplasma infections (OR=31.67, CL=8.63-116.16, $p<0.001$) with a preponderance of *M. fermentans* infections (50% of patients, OR=59.0, CL=7.55-460, $p<0.001$), whereas the most commonly found *Mycoplasma* spp. in CFS patients without Lyme Disease was *M. penumoniae* (34% of patients. OR=14.94. CL=3.25-68.73, $p<0.001$). .

Multiple Systemic Infections Some Summary Points

- Systemic chronic infections (viral, bacterial) are **commonly found** in various chronic diseases
- The **numbers** of different chronic infections (viral, bacterial) are **linked to symptom severities** of the disease (morbidity)
- Some chronic infections (viral, bacterial, fungal) are **linked to specific exposures** (ie, Gulf War Illness)
- **Other events** (chemicals, heavy metals, other environmental exposures) could also be necessary

Cell



Chronic Infections cause damage to Cellular membranes, especially lipids

Example:
Pathogenic Mycoplasmas

Mycoplasma host mimick antigens

Host cell antigens

Mycoplasma super antigens

1. Release of toxins
2. Competes for metabolites
3. Alters cellular structures
4. Releases host antigens
5. Stimulates ROS/RNS

Prof. Garth L. Nicolson
The Institute for Molecular Medicine

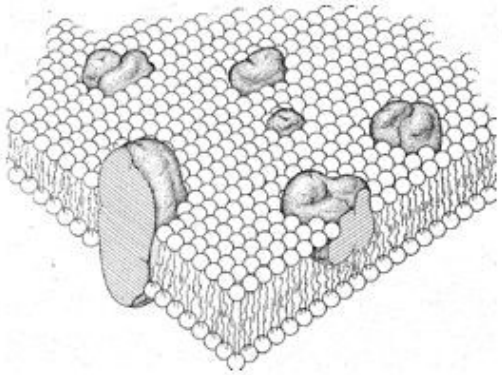
Use of Membrane Lipid Replacement to Repair and Replace Damaged, Oxidized Membrane Glycerolphospholipids in Order to Restore Function

Fluid-Mosaic Membrane Model (1972)

S.J. Singer, G.L. Nicolson, Science 175: 720-731 (1972)

The Fluid Mosaic Model of the Structure of Cell Membranes

Cell membranes are viewed as two-dimensional solutions of oriented globular proteins and lipids.



S. J. Singer and Garth L. Nicolson

Membrane Thermodynamics
Lipid Bilayer/Globular Integral Proteins
Integral-v-Peripheral Proteins
Mobility of Membrane Components
Maintenance of Membrane Asymmetry

Special Issue of BBA Biomembranes (2014)

Biochimica et Biophysica Acta 1838 (2014) 1451–1466

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Review

The Fluid—Mosaic Model of Membrane Structure: Still relevant to understanding the structure, function and dynamics of biological membranes after more than 40 years ☆,☆☆

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Membrane lipids
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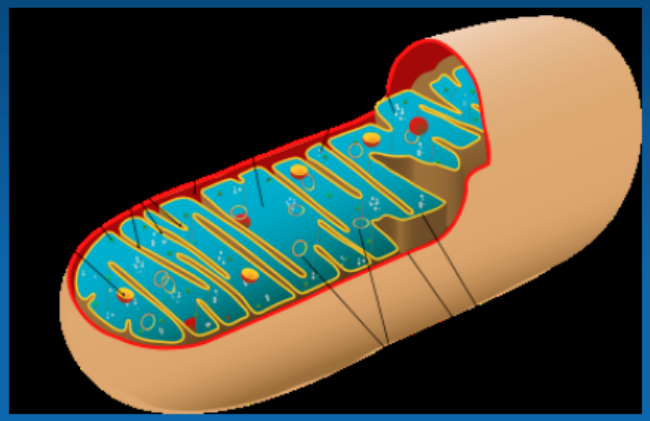
Membrane dynamics

ABSTRACT

In 1972 the Fluid—Mosaic Membrane Model of membrane structure was proposed based on thermodynamic principals of organization of membrane lipids and proteins and available evidence of asymmetry and lateral mobility within the membrane matrix [S. J. Singer and G. L. Nicolson, Science 175 (1972) 720–731]. After over 40 years, this basic model of the cell membrane remains relevant for describing the basic nano-structures of a variety of intracellular and cellular membranes of plant and animal cells and lower forms of life. In the intervening years, however, new information has documented the importance and roles of specialized membrane domains, such as lipid rafts and protein/glycoprotein complexes, in describing the macrostructure, dynamics and functions of cellular membranes as well as the roles of membrane-associated cytoskeletal fences and extracellular matrix structures in limiting the lateral diffusion and range of motion of membrane components. These newer data build on the foundation of the original model and add new layers of complexity and hierarchy, but the concepts described in the original model are still applicable today. In updated versions of the model more emphasis has been placed on the mosaic nature of the macrostructure of cellular membranes where many protein and lipid

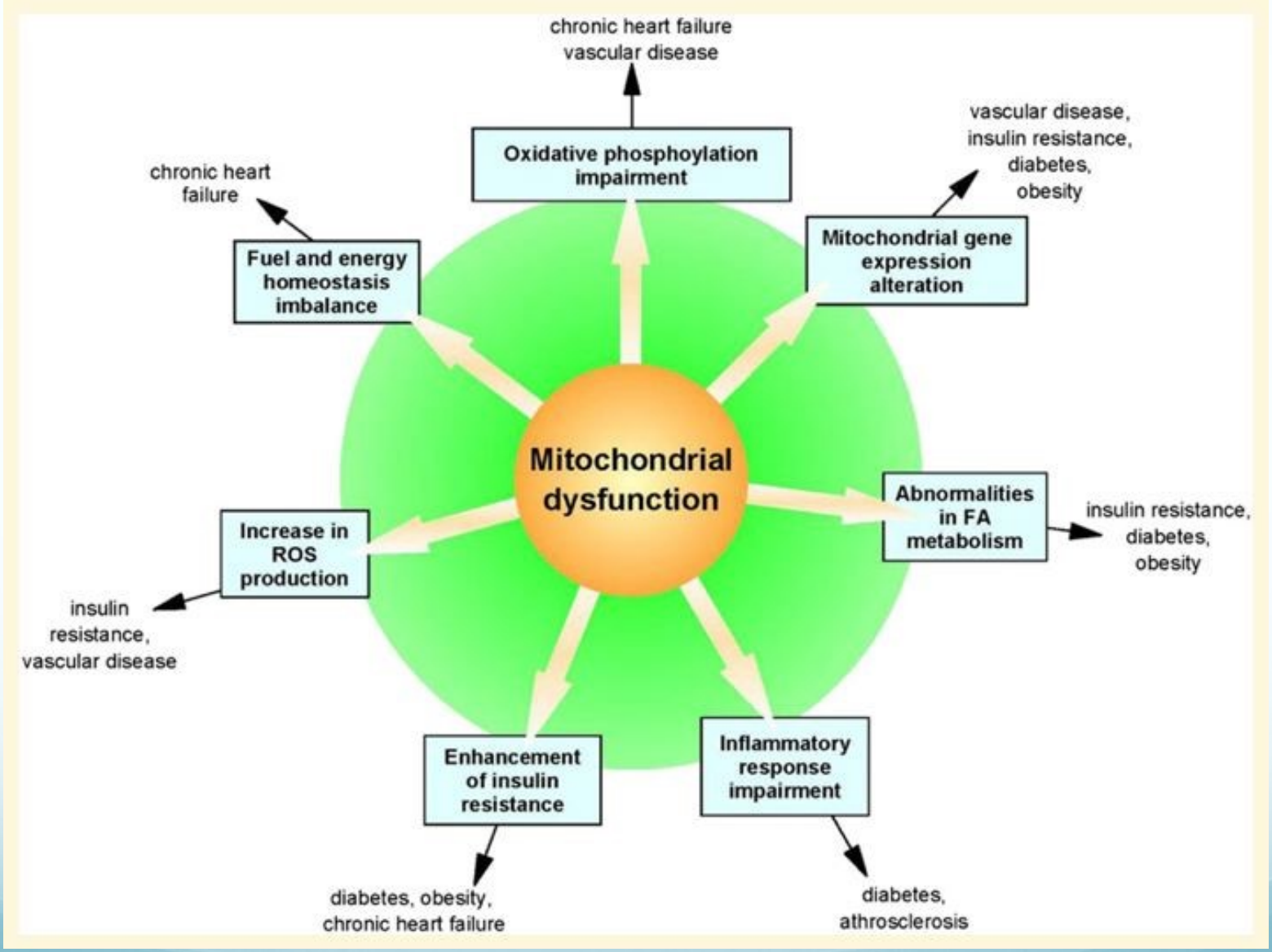
Membrane Lipid Replacement for Restoring Mitochondrial Function

Mitochondria and Cellular Health

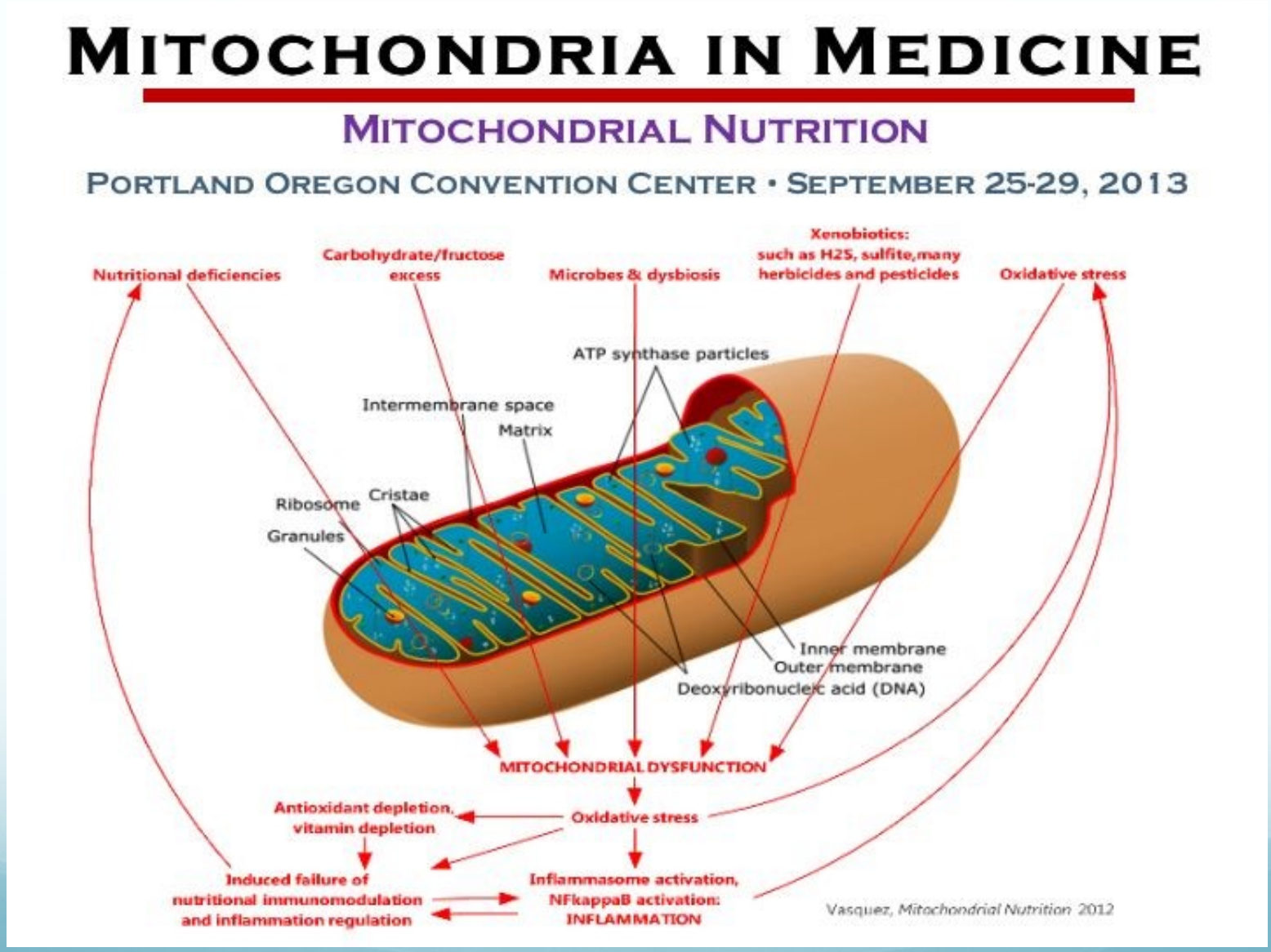


ATP production
Lipid metabolism
ROS/RNS production
Calcium homeostasis
Autophagy, mitophagy
Apoptosis, pyroptosis
Inflammasomes
NODs, DAMPs, PAMPs

Mitochondrial Dysfunction and Chronic Disease



Mitochondria Dysfunction and Disease



Treatments for Mitochondrial Dysfunction have been Targeted to Mitochondria for:

- Loss of maintenance of inner membrane electrical and chemical trans-membrane potential
- Alterations in Electron Transport Chain function
- Reduction in transport of critical metabolites into mitochondria
- Other events that may also be important, such as mtDNA genetics, chemical exposures, heavy metals, etc., for mitochondrial dysfunction

Mitochondrial Natural Supplements

Alternative Therapies in Health and Medicine 2014; 20(Suppl 1): 18-25.

ORIGINAL RESEARCH

Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements

Garth L. Nicolson, PhD

ABSTRACT

Loss of function in mitochondria, the key organelle responsible for cellular energy production, can result in the excess fatigue and other symptoms that are common complaints in almost every chronic disease. At the molecular level, a reduction in mitochondrial function occurs as a result of the following changes: (1) a loss of maintenance of the electrical and chemical transmembrane potential of the inner mitochondrial membrane, (2) alterations in the function of the electron transport chain, or (3) a reduction in the transport of critical metabolites into mitochondria. In turn, these changes result in a reduced efficiency of oxidative phosphorylation and a reduction in production of adenosine-5'-triphosphate (ATP). Several components of this system require routine replacement, and this need can be facilitated with natural supplements. Clinical trials have shown the utility of using oral replacement supplements, such as L-carnitine, alpha-lipoic acid (α-lipoic acid [1,2-dithiolane-3-pentanoic acid]), coenzyme Q_{10} (CoQ_{10} [ubiquinone]), reduced nicotinamide adenine dinucleotide (NADH), membrane phospholipids, and other supplements. Combinations of these supplements can reduce significantly the fatigue and other symptoms associated with chronic disease and can naturally restore mitochondrial function, even in long-term patients with intractable fatigue. (*Altern Ther Health Med.* 2014;20 (suppl 1):18-25.)

Membrane Lipid Replacement Therapy

International Journal of Clinical Medicine, 2016, 7, 133-143
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2016.72015

Scientific Research Publishing

Membrane Lipid Replacement: Clinical Studies Using a Natural Medicine Approach to Restoring Membrane Function and Improving Health

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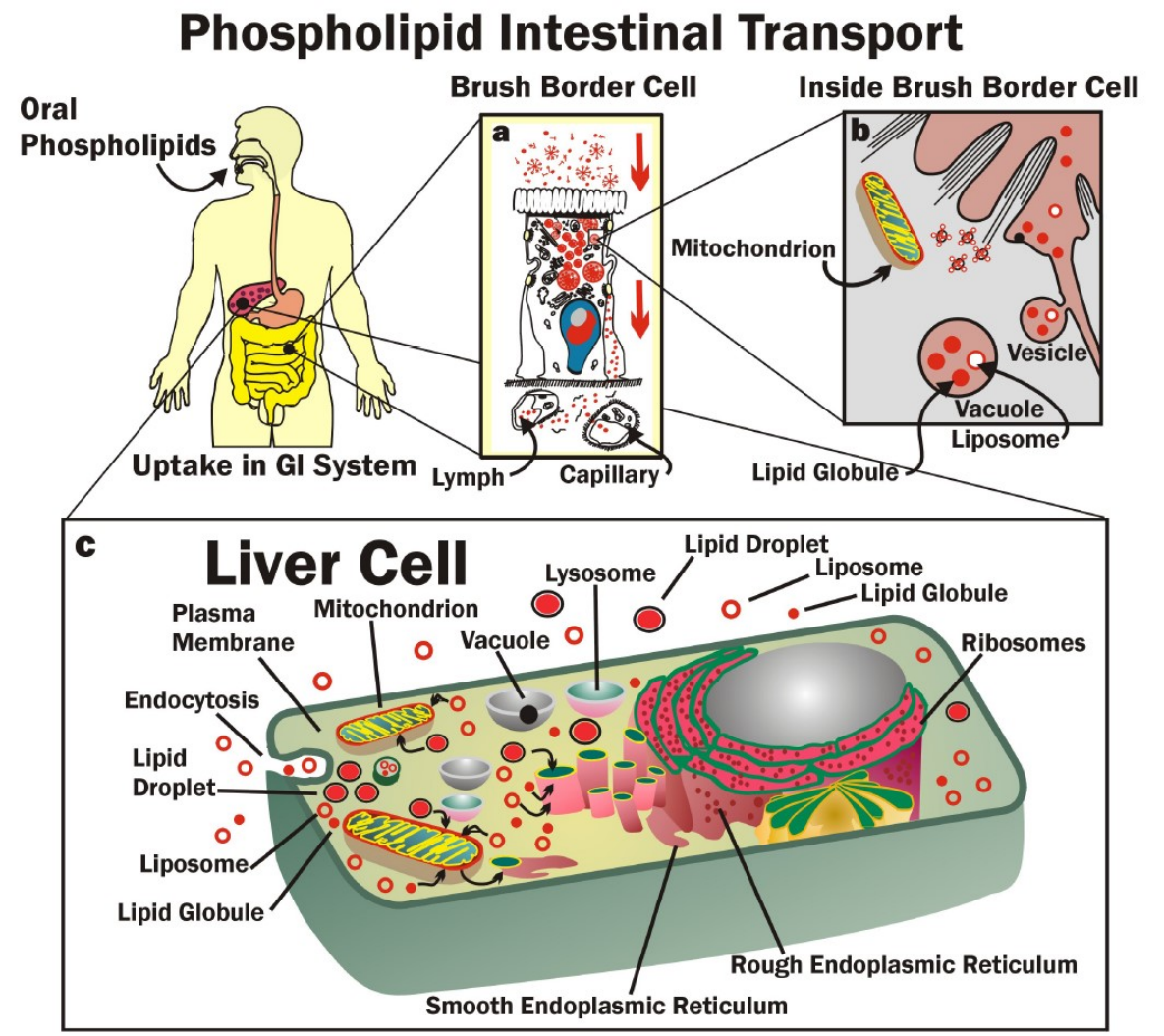
Received 5 January 2016; accepted 17 February 2016; published 22 February 2016

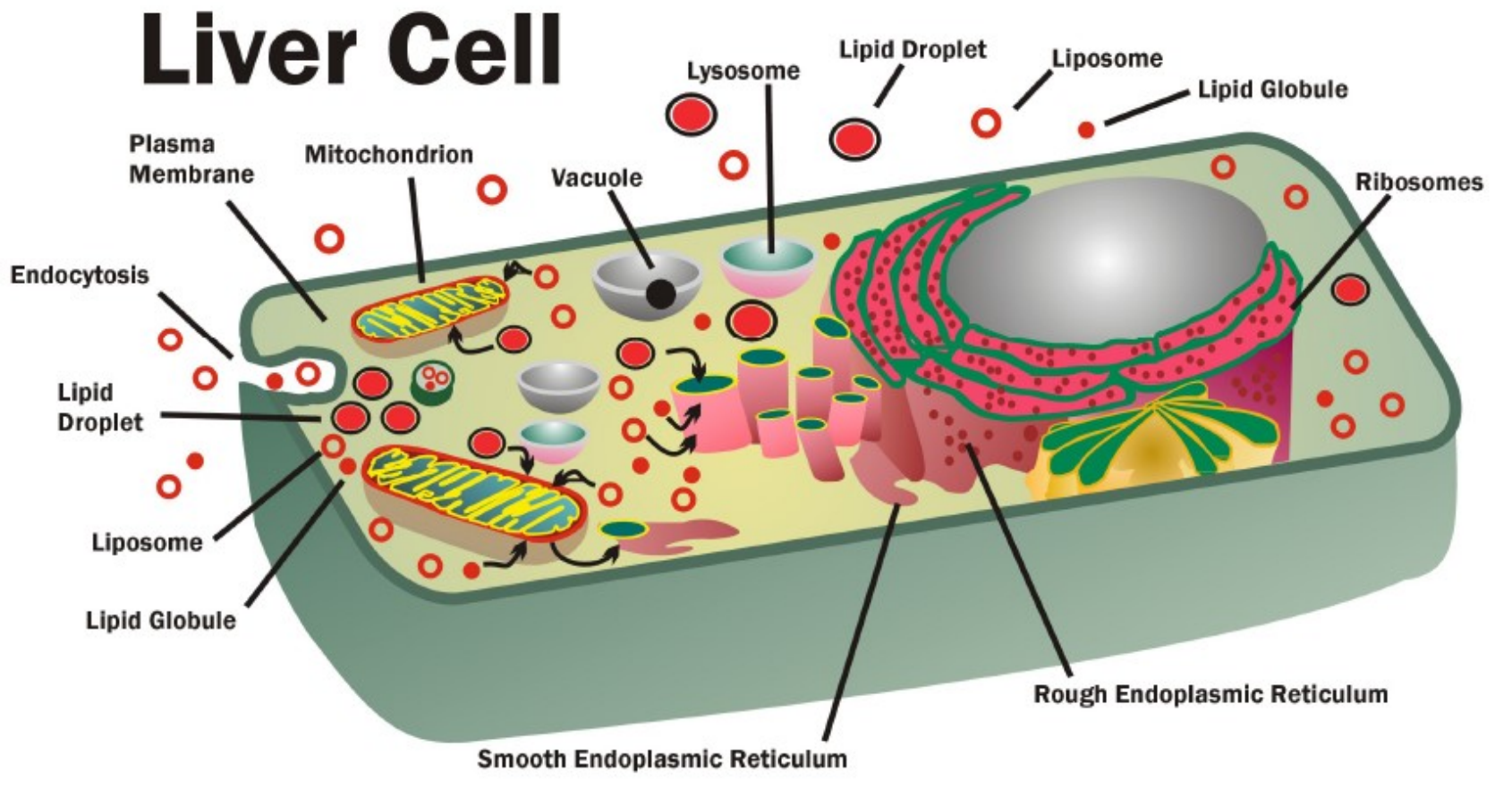
What is Membrane Lipid Replacement Therapy?

- What is Oral Membrane Lipid Replacement Therapy (MLRT)?
- MLRT is the use of membrane glycerolphospholipids (PC, PE, PS, PI, PG, etc.) with unsaturated Fatty Acids to replace damaged membrane phospholipids and restore function (example=NTFactor®).
- MLRT has also been used in formulations with CoQ_{10} and other ingredients (NADH, L-carnitine, α-keto-glutaric acid, and others) (example=ATP Fuel®).

Glycerolphospholipid Transport in the Gut



Lipid Globules, Droplets, Liposomes and Lipoproteins



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DISCOVERIES 2016, Jan-Mar, 4(1): e54
DOI: 10.15190/d.2016.1

PERSPECTIVE Article

Clinical Uses of Membrane Lipid Replacement Supplements in Restoring Membrane Function and Reducing Fatigue in Chronic Diseases and Cancer

Garth L. Nicolson,[1] Steven Rosenblatt[2], Gonzalo Ferreira de Mattos[3], Robert Settineri[4], Paul C. Breeding[5], Rita R. Ellithorpe[6], Michael E. Ash[7]*

[1]The Institute for Molecular Medicine, Huntington Beach, California 92647, USA; [2]Saint John's Health Center, Santa Monica, CA, USA; [3]Laboratory of Ion Channels, School of Medicine, Universidad de la República, Montevideo, Uruguay, [4]Sierra Productions Research, Irvine, CA, USA; [5]Blue Hole Wellness, Wimberley, TX, USA; [6]Tustin Longevity Center, Tustin, CA, USA; [7]Clinical Education, Newton Abbot, Devon, UK.

Table 1. Clinical trials and effects of NTFactor® MLR supplements on fatigue scores.

MLR Supplment	Subjects/patients	No. of patients	Av. age	Time (weeks)	Reduction (%)[b]	Reference
Propax/NTFactor®	Chronic fatigue	34	50.3	8	40.5[§]	Ellithorpe et al. [36]
NTFactor®	Aging, chronic fatigue	22	68.9	12	35.5*	Agadjanyan et al. [37]
NTFactor®	CFS/fibromyalgia	15	44.8	8	43.1*	Nicolson & Ellithorpe [38]
Healthy Curb®	Obesity, fatigue	35	42	8	23.9*	Ellithrope et al. [39]
APF/NTFactor®[c]	Aging, chronic fatigue	67	57.3	1	36.8[§]	Nicolson et al. [40]
Propax/NTFactor®	Cancer, fatigue	35	50.7	8	30.1*	Nicolson [3]
ATP Fuel®/NTFactor®	CFS/ME	30	55	8	30.7[§]	Nicolson et al. [23,41]
ATP Fuel®/NTFactor® GW	GW Illness, fatigue	16	42.2	8	34.6*	Nicolson et al. [23]
ATP Fuel®/NTFactor®	Lyme disease, fatigue	17	52.4	8	26.0*	Nicolson et al. [42]

[a]Modified from Nicolson[3]

[b]Piper Fatigue Scale[43]

[c]Advanced Physician's Formula with NTFactor®

[§]$p<0.0001$, *$p<0.001$ t-test with/without NTFactor®

Av. - Average; CFS - chronic fatigue syndrome; ME - myalgic encephalomyelitis;; GW – Gulf War;

Nicolson et al., Discoveries 2016; 4(1): e54.

Membrane Lipid Replacement Therapy Clinical Trials (4 of 7 trials shown)

NTFactor Clinical Trials Summ.

Condition or Illness	Average Age	Piper Fatigue	Significance
Aging, Fatigue	70	35.5% reduction	P<0.001
Chronic Fatigue	50.3	40.5% reduction	P<0.0001
CFS FMS	44.8	43.1% reduction	P<0.0001
Aging, Fatigue	57.3	36.8% in one week	P<0.0001

Membrane Lipid Replacement Therapy and Mitochondrial Function in CFS/FM Patients

J Chronic Fatigue Syndr 2003; 11(3): 23-36

Nutritional Supplement (NT Factor™) Restores Mitochondrial Function and Reduces Moderately Severe Fatigue in Aged Subjects

Michael Agadjanyan, PhD[1], Vitaley Vasilevko, PhD[1], Anahit Ghochikyan, PhD[1],

Paul Berns, MD[1], Patrick Kesslak, Ph.D.[2],

Robert A. Settineri, MS[3], and Garth L. Nicolson, PhD[1]

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2. The Institute of Brain Aging and Dementia, University of California, Irvine, CA 92467
3. Research Consultant, Nutritional Therapeutics, Inc., Hauppauge, NY

ABSTRACT

OBJECTIVE: Decreased mitochondrial function is a characteristic of aging and fatigue. Here we determined if mild to moderately severe fatigue in a group of aged subjects (mean age >60 years), as defined by the validated Piper Fatigue Scale (PFS), can be significantly improved by use of a glycophospholipid dietary supplement, NT Factor™

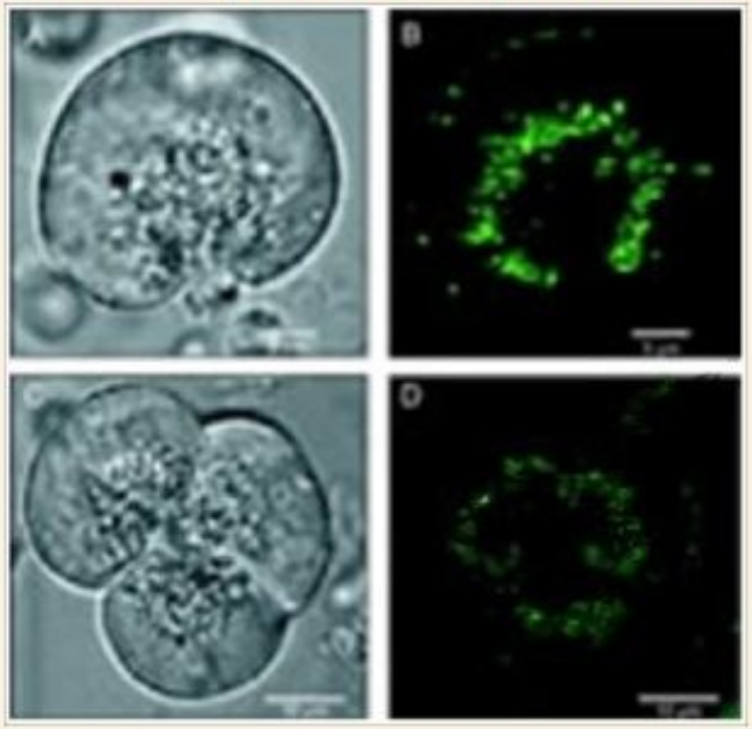
Mitochondrial Function Assay (inner membrane trans-membrane potential)

- Rhodamine 123 uptake into mitochondrial and its fluorescence is a direct measure mitochondrial function and inner membrane transmembrane electrical and chemical potential.
- Mitochondria are isolated from blood leukocytes of aged subjects, and Rh123 is added to the sample.
- Mitochondrial function is determined by cellular fluorescence on a FACS instrument.

Mitochondrial Function Assay

Rhodamine 123 Redox Dye Mitochondrial Fluorescence (Active Mitochondria)

Healthy Cell phase contrast



Healthy Cell fluorescence

CFS/ME Cell phase contrast

CFS/ME Cell fluorescence

The ME/CFS cell shows less fluorescent intensity because the mitochondria are damaged

MLR Cross-Over Trial

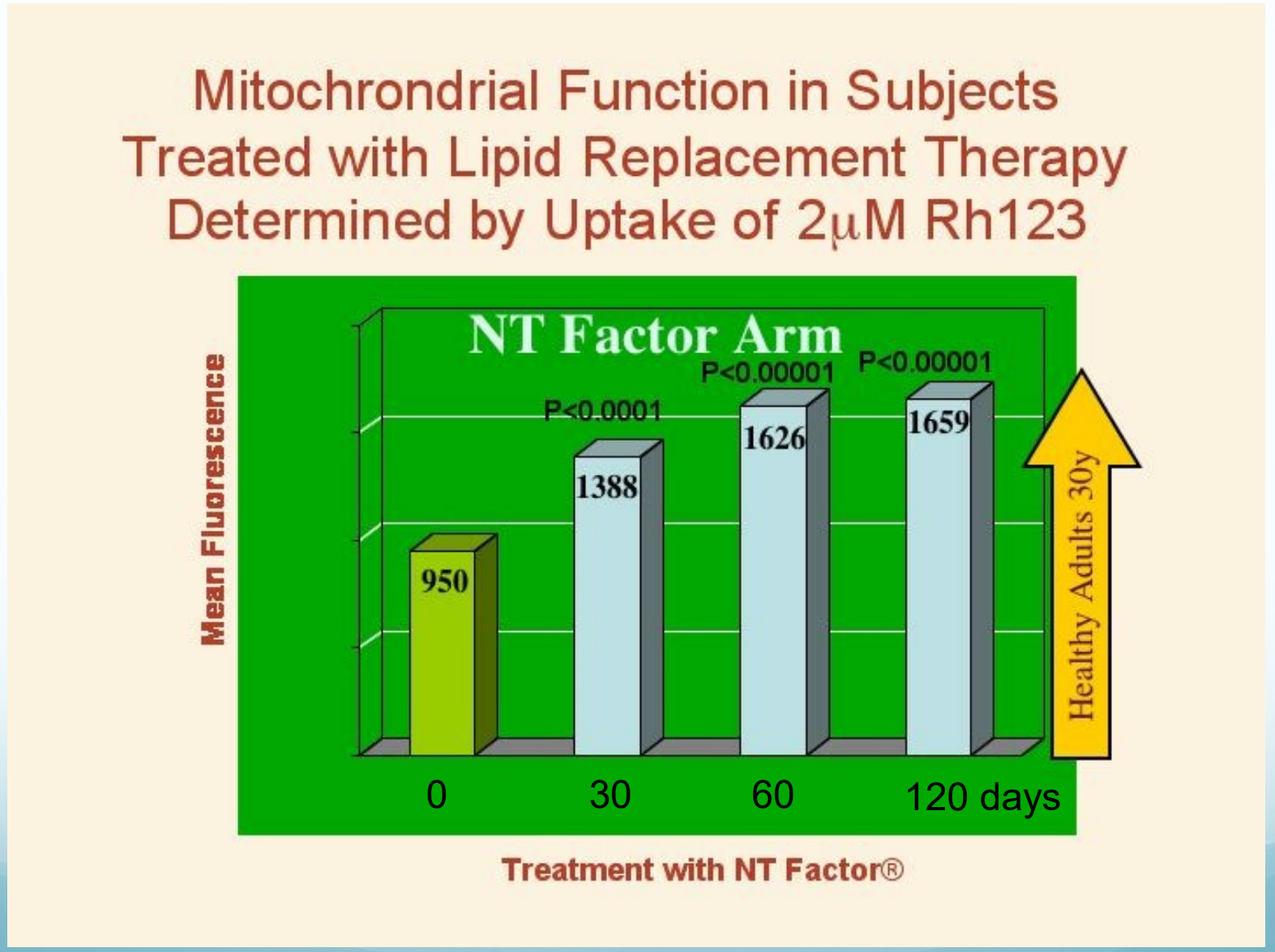
Design of a Cross-Over Clinical Trial

LRT THERAPY ⟹ WASHOUT ⟹ PLACEBO

PLACEBO ⟹ WASHOUT ⟹ LRT THERAPY

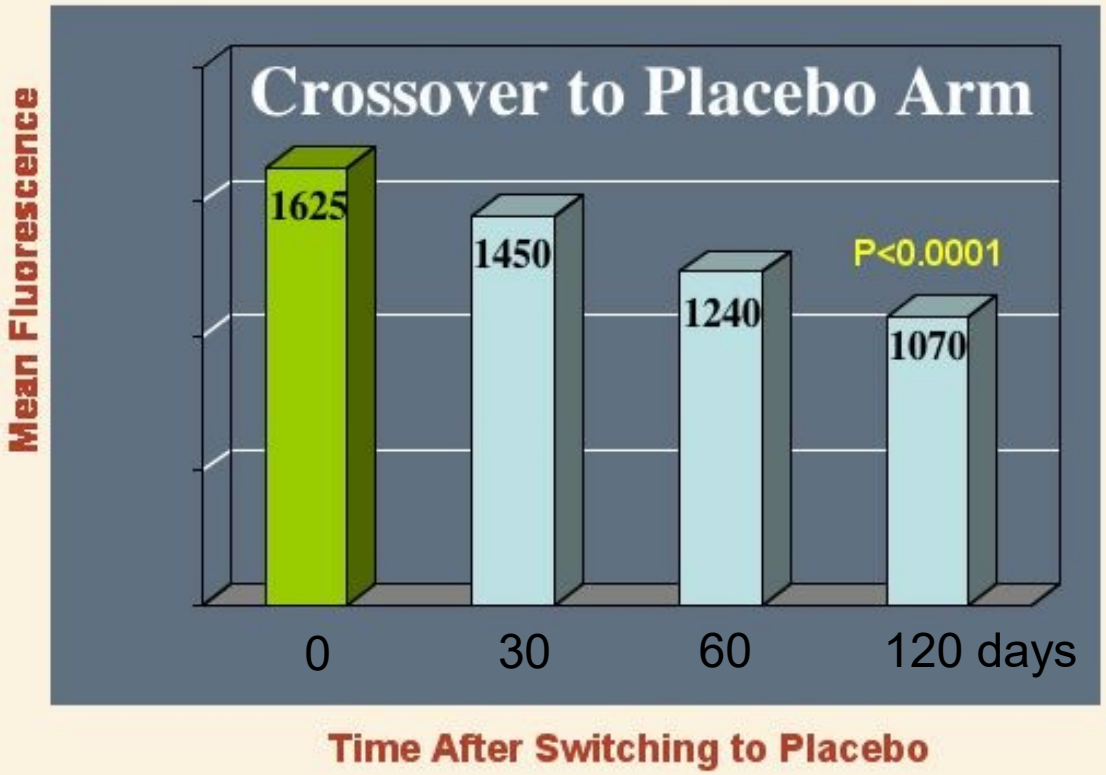
CFS and CFS/FM Patients

MLR Cross-over Clinical Trial (NTFactor)



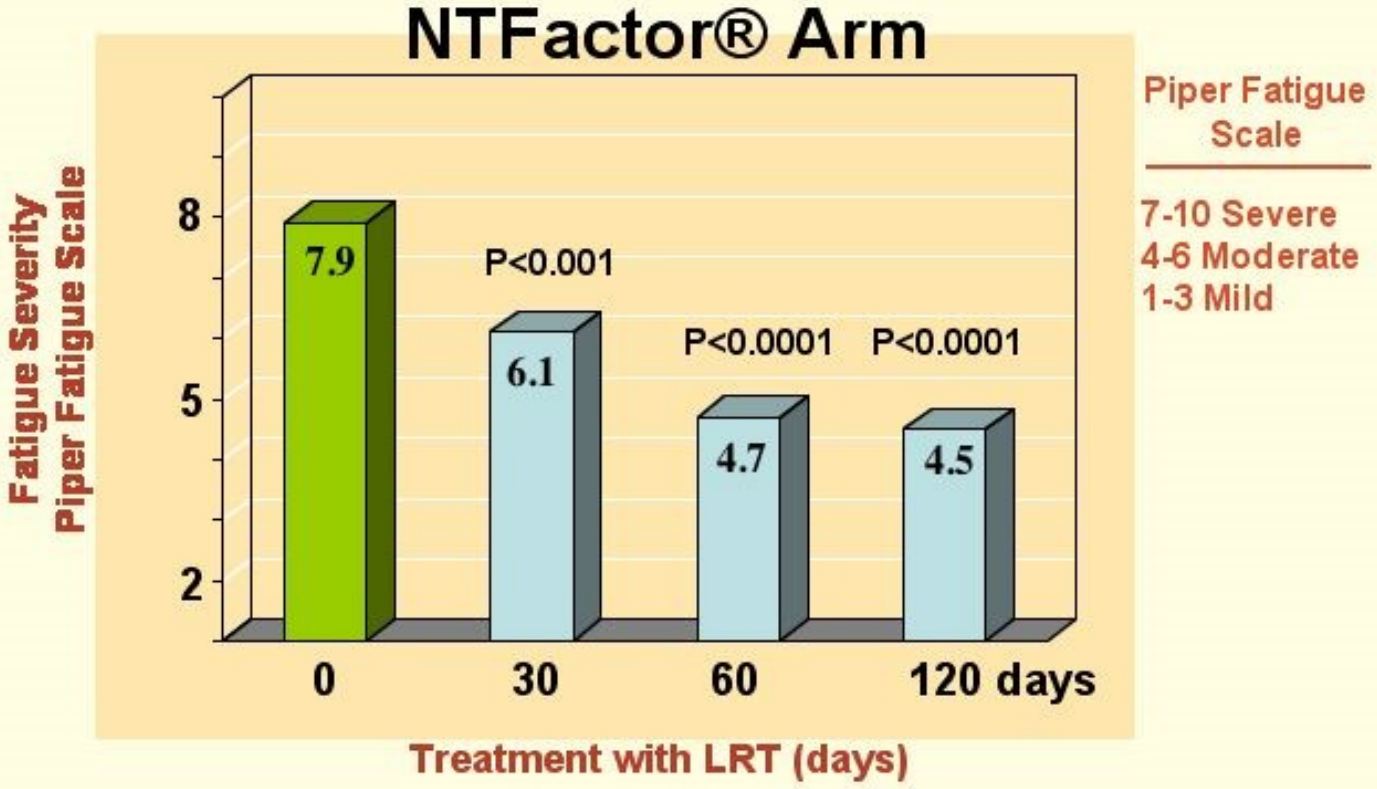
MLR Cross-over Clinical Trial (NTFactor)

Mitochrondrial Function in Subjects Treated with LRT then Placebo Determined by Uptake/FL of 2μM Rh123

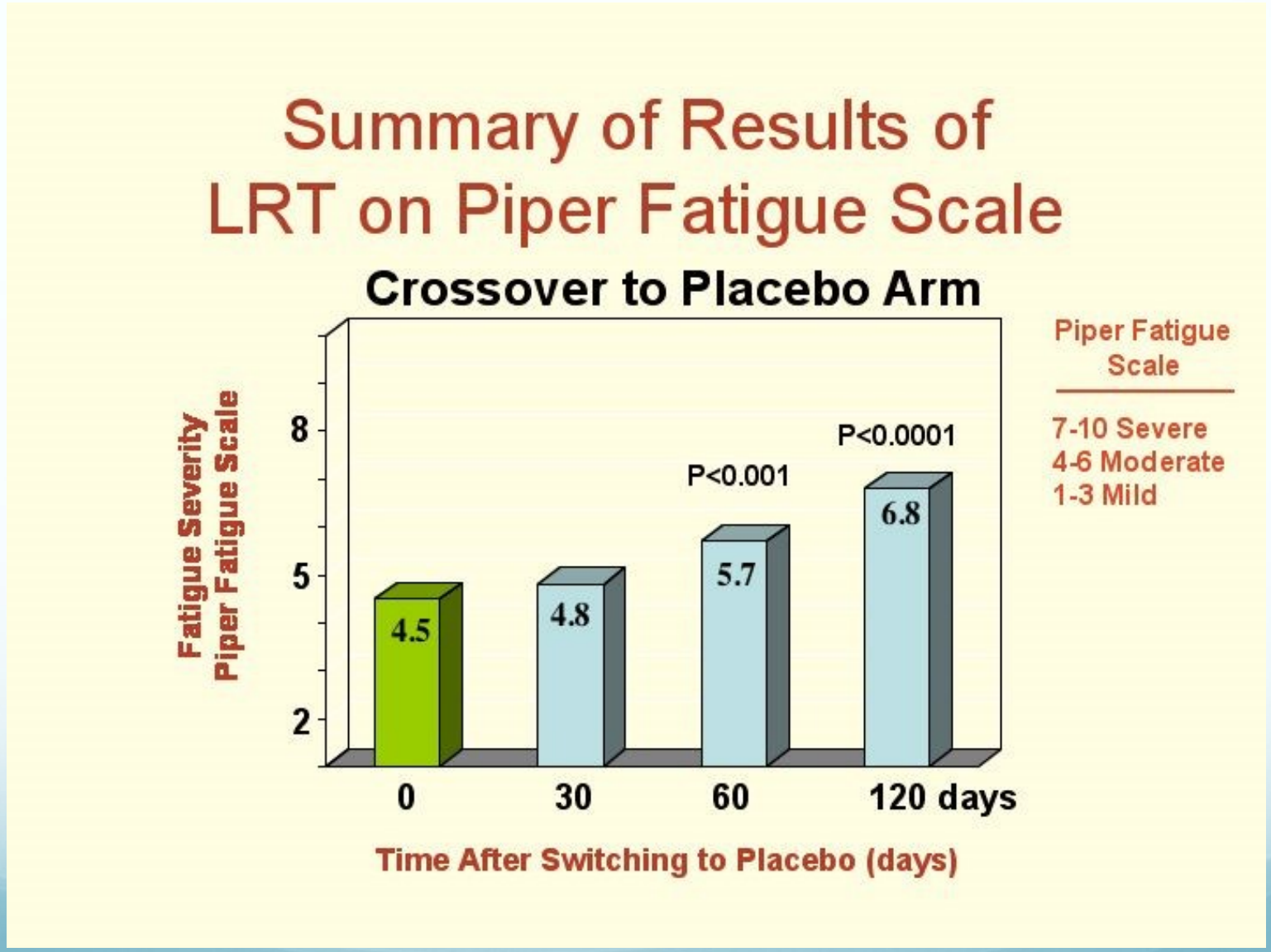


MLR Cross-over Clinical Trial (NTFactor)

Summary of Results of LRT on Piper Fatigue Scale



MLR Cross-over Clinical Trial (NTFactor)



Pain in Fibromyalgia Preliminary Effects of MLR

Pain Assessment after 3 weeks of MLR with NTFactor Lipids

(4 grams of NTFactor Lipids, Patented Energy wafers)

Yale Multidimensional Pain Inventory (MPI)

42% reduction in MPI score

Wisconsin Brief Pain Inventory (BPI)

37.5% reduction in BPI score

Reduction of Peripheral Pain in Fibromyalgia by MLR

- Normalization of Peripheral Nerve Resting Potentials
- Effects on Nerve Junctions
- Reduction of Peripheral Inflammatory Cytokines
- Effects on Peripheral Microcirculation
- Effects on Gastrointestinal Permeability

Pro-Inflammatory Cytokines in FM

PLOS | ONE

RESEARCH ARTICLE

Comparison of the Levels of Pro-Inflammatory Cytokines Released in the Vastus Lateralis Muscle of Patients with Fibromyalgia and Healthy Controls during Contractions of the Quadriceps Muscle – A Microdialysis Study

Nikolaos Christidis[1]*, Bijar Ghafouri[2], Anette Larsson[3,5], Annie Palstam[4], Kaisa Mannerkorpi[3,4,5], Indre Bileviciute-Ljungar[6], Monika Löfgren[6], Jan Bjersing[3], Eva Kosek[7], Björn Gerdle[2], Malin Ernberg[1]

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Citation: Christidis N, Ghafouri B, Larsson A, Palstam A, Mannerkorpi K, Bileviciute-Ljungar I, et al. (2015) Comparison of the Levels of Pro-Inflammatory Cytokines Released in the Vastus Lateralis Muscle of Patients with Fibromyalgia and Healthy Controls during Contractions of the Quadriceps Muscle – A Microdialysis Study. PLoS ONE 10(12): e0143856. doi:10.1371/journal.pone.0143856

Microcirculation in FM Patients

ARTHRITIS & RHEUMATISM
Vol. 43, No. 12, December 2000, pp 2823–2833

REGIONAL CEREBRAL BLOOD FLOW IN FIBROMYALGIA

Single-Photon–Emission Computed Tomography Evidence of Reduction in the Pontine Tegmentum and Thalami

RICHARD KWIATEK, LEIGHTON BARNDEN, RAYMOND TEDMAN, RICHARD JARRETT, JENNI CHEW, CHRISTOPHER ROWE, and KEVIN PILE

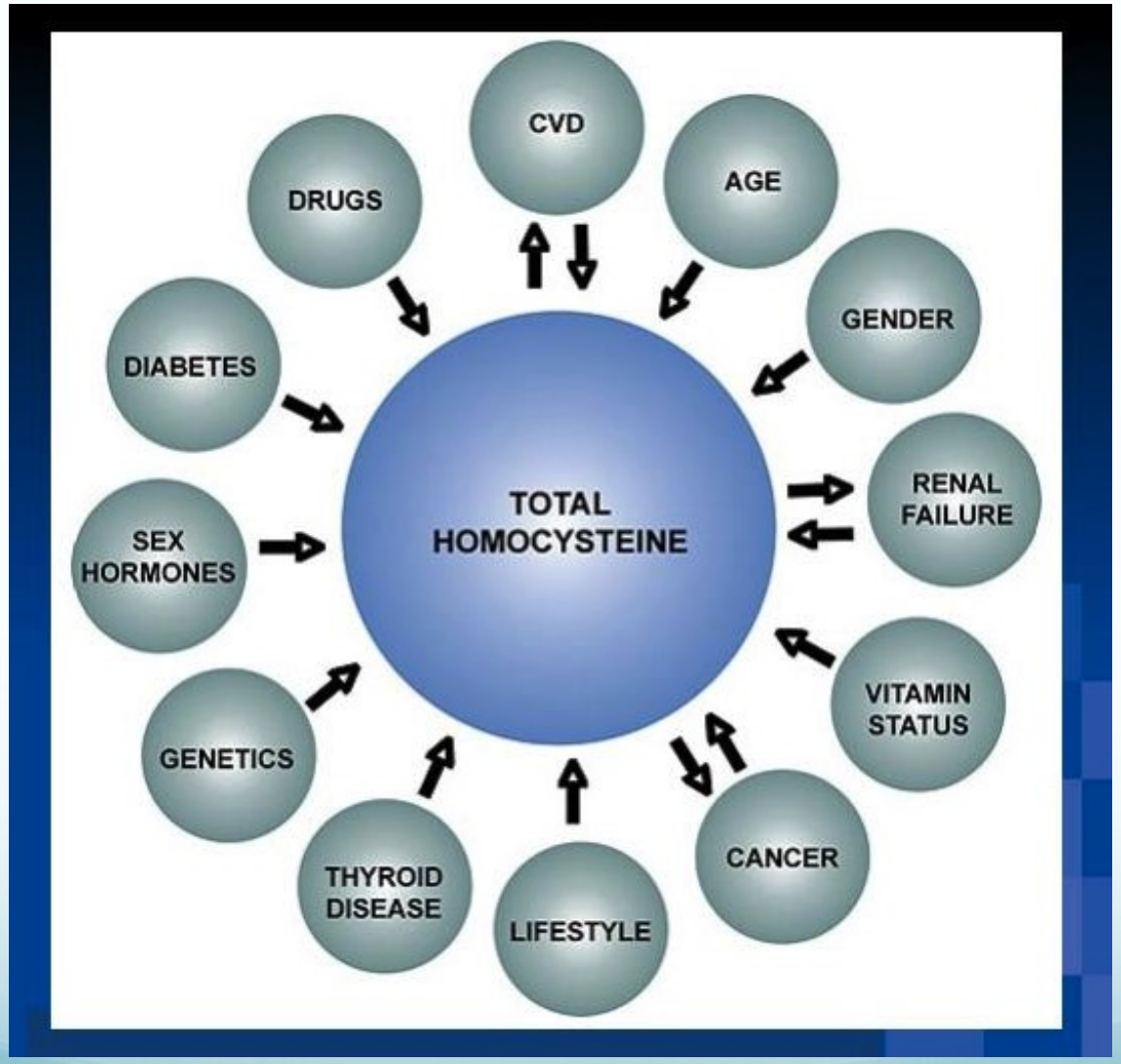
Objective. **To determine whether regional cerebral blood flow (rCBF) is abnormal in any cerebral structure of women with fibromyalgia (FM), following a report that rCBF is reduced in the thalami and heads of caudate nuclei in FM.**

Methods. **Seventeen women with FM and 22 healthy women had a resting single-photon–emission computed tomography (SPECT) brain scan to assess rCBF and a T1-weighted magnetic resonance imaging**

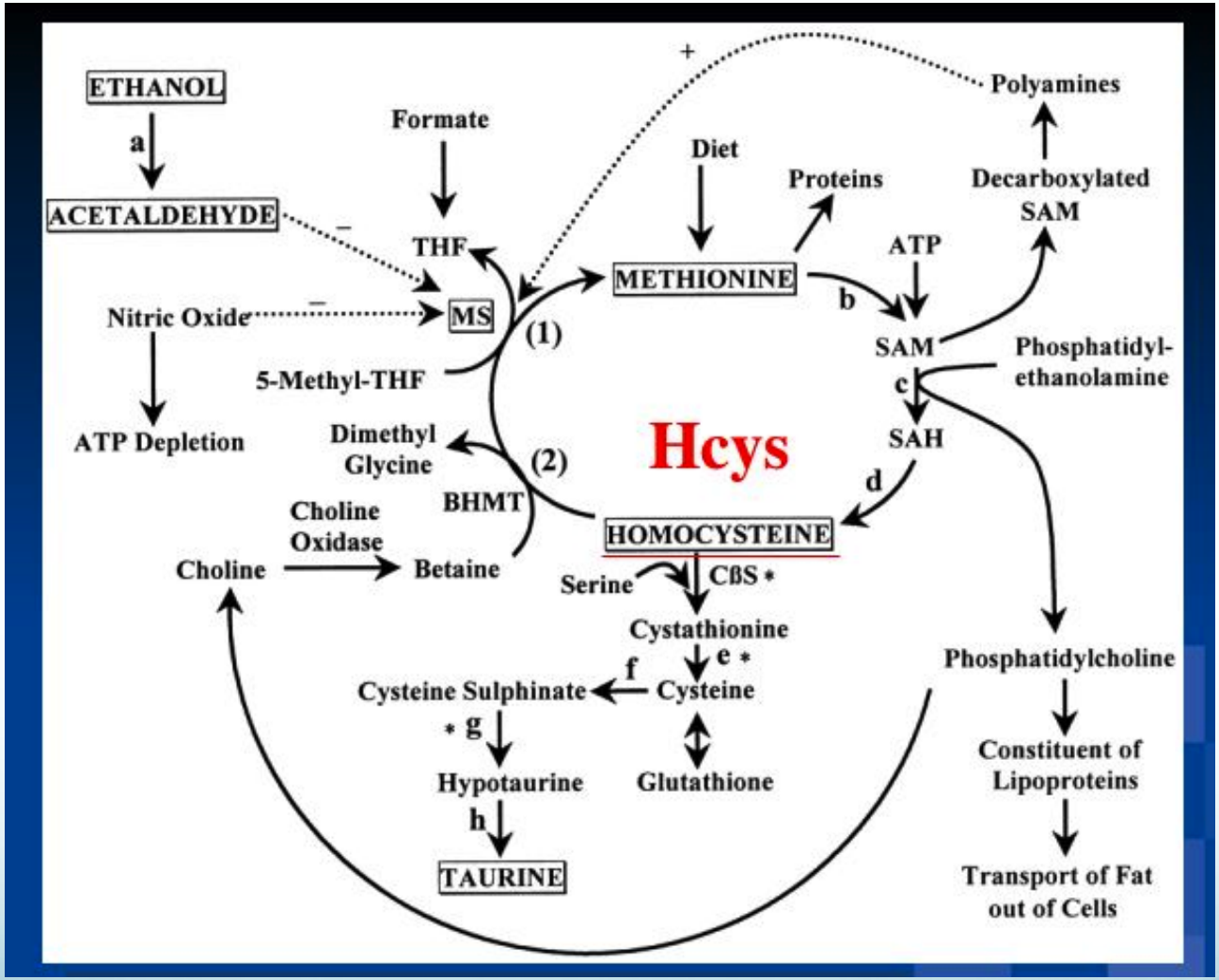
nucleus. No correlations were found with clinical features or indices of pain threshold.

Conclusion. **Our finding of a reduction in thalamic rCBF is consistent with findings of functional brain imaging studies of other chronic clinical pain syndromes, while our finding of reduced pontine tegmental rCBF is new. The pathophysiologic significance of these changes in FM remains to be elucidated.**

Homocyteine Levels Associated with:



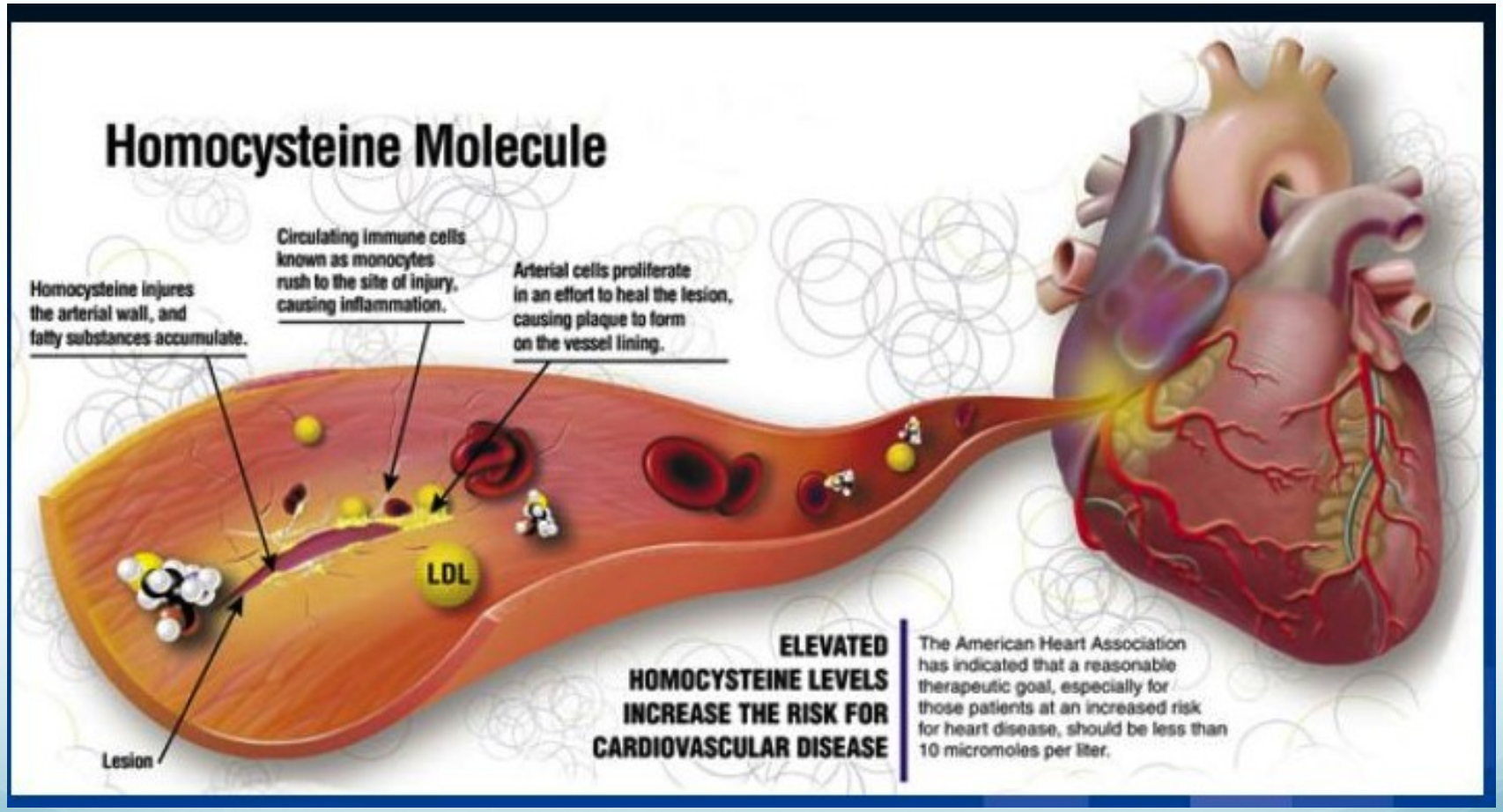
Homocysteine-Methionine Cycle



High Homocyteine Blood Levels are Risk Factors for:

- Cardiovascular Diseases
- Stroke and Brain Diseases
- Birth Defects
- Alzheimer's Disease and Dementia
- Autism Spectrum Disorders
- Renal Failure
- Type 2 Diabetes
- Macular Degeneration
- Osteoporosis

Homocysteine Levels and CVD



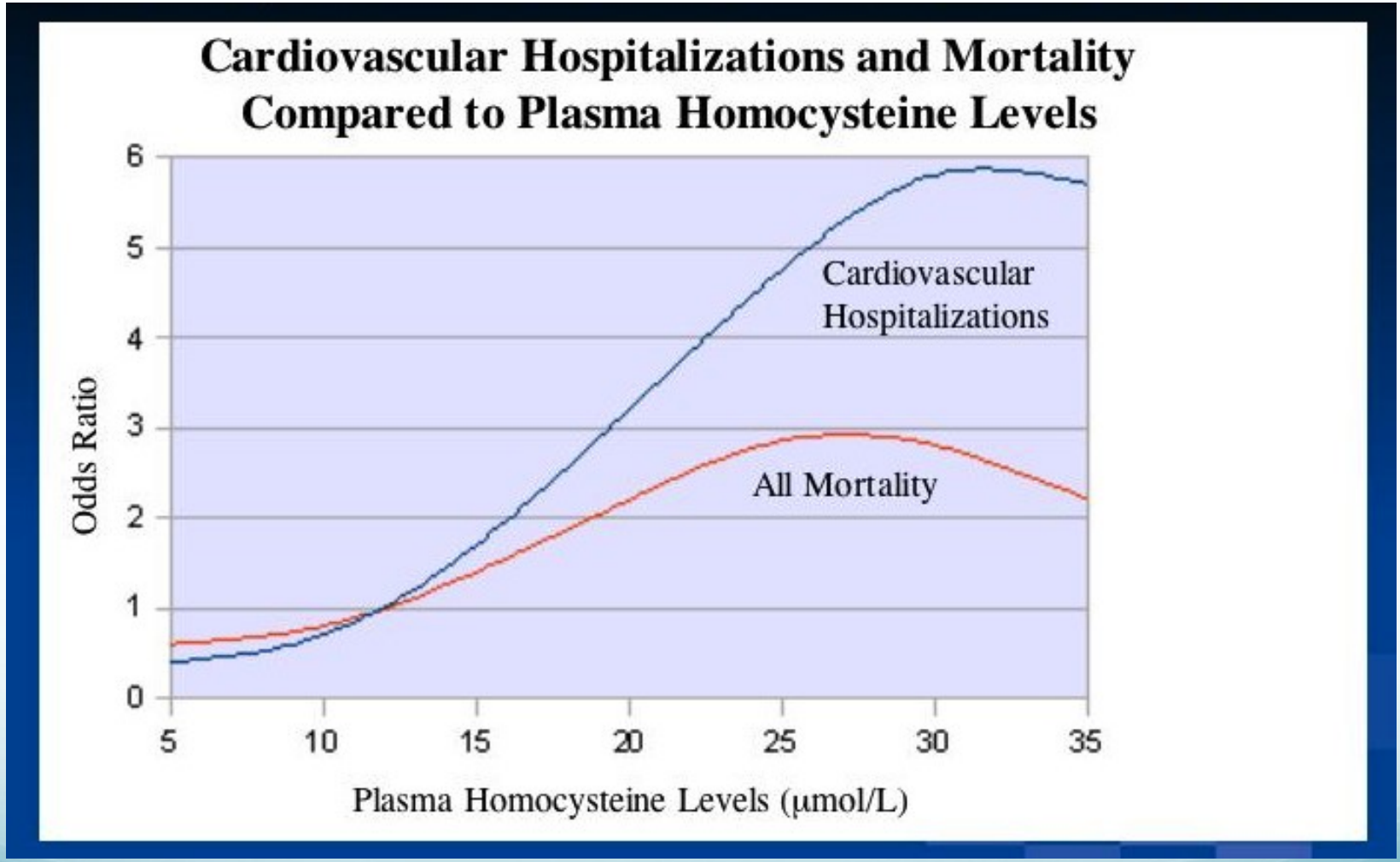
Homocysteine and CVD Risk

Homocysteine Levels and Cardiovascular Disease

Above **10.8** micromoles per Liter = **Increased Risk CVD**

Washio, T. et al. Relationship between plasma homocysteine levels and congestive heart failure in patients with acute myocardial infarction. *International Heart Journal* 2012; 52: 224-228.

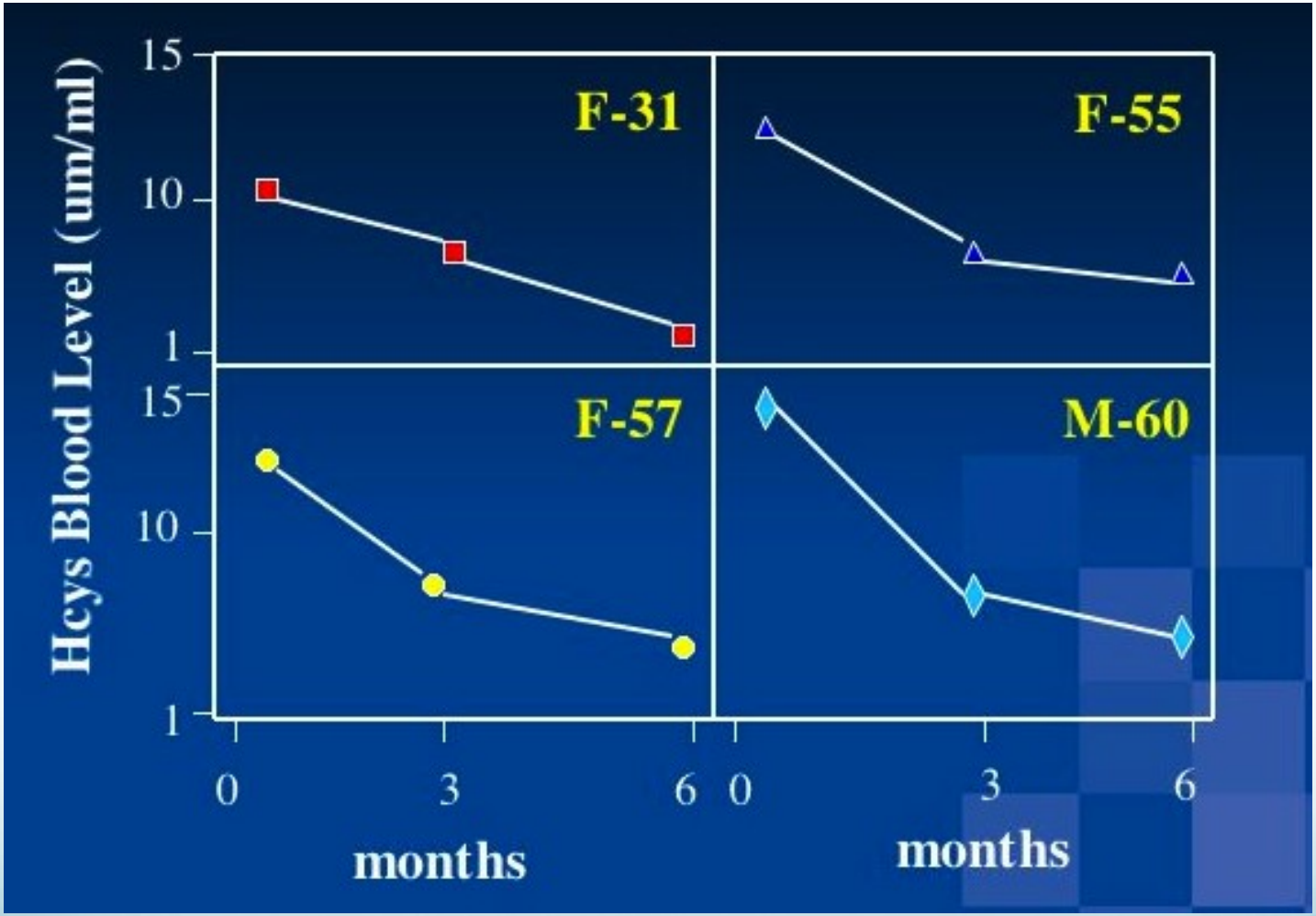
Homocysteine Levels and CVD



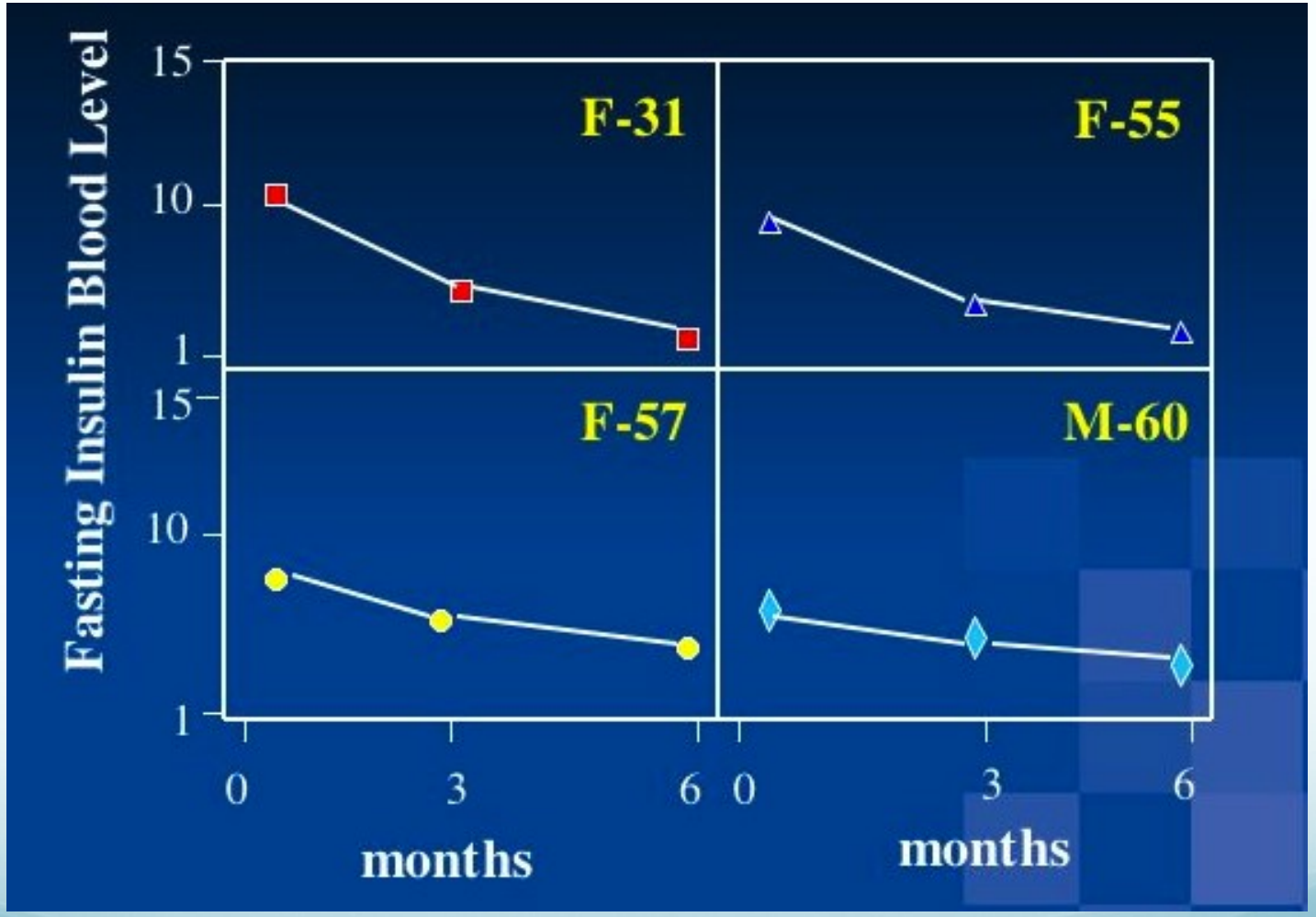
MLR and Homocysteine

- Retrospective Study with 35 random patients (28 F, 7 M) of average age = 60.7 who were on NTFactor (2 g/day) for 6 months.
- Blood Chemistry: Hcys, fasting insulin, Erythrocyte Sed Rate, HDL, LDL, BUN, GGT, SGPT, ALP, CRP, K, Na, triglycerides, Fe, creatine, cortisol, etc.
- Blood taken every 2 months for 6 months.
- Patient assessments every 2 months.

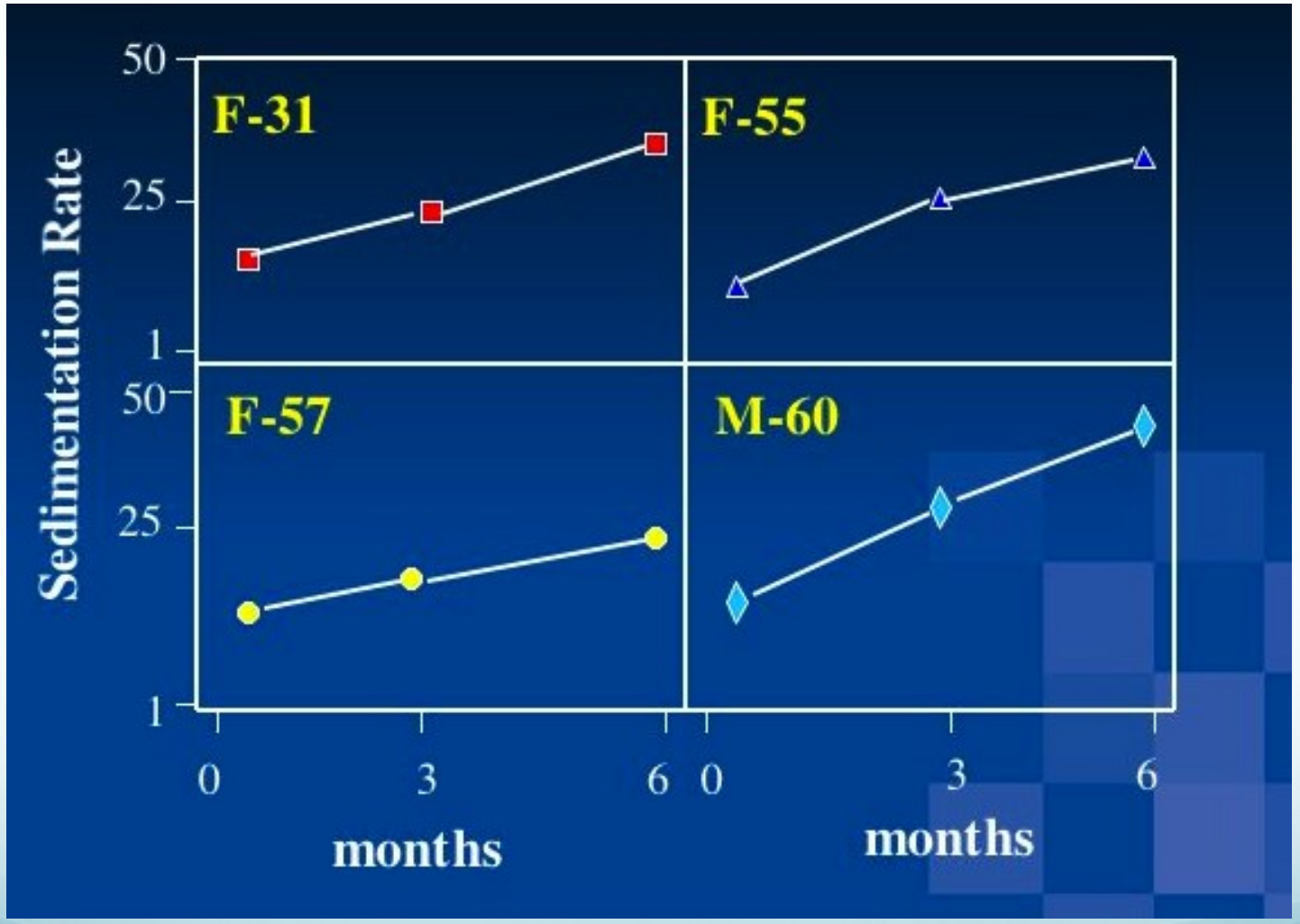
Homocysteine Blood Levels



Fasting Insulin Blood Levels



Erythrocyte SED Rate



Blood Parameters on MLR for 6 Mo

- Homocysteine (lowers mean **11.85 to 7.40**, $p<0.001$)
- Fasting Insulin (lowers mean **12.8 to 5.3**, $p<0.001$)
- Erythrocyte SED (improves mean **10.5 to 20.19**, $p<0.003$)
- HDL (lowers mean **65.2 to 60.3**, $p<0.05$)
- LDL (increases mean **115.7 to 121.1**, $p<0.09$)
- CRP (lowers mean **2.91 to 2.02**, $p<0.05$)
- All other blood chemistry changes were **Not Significant**
- No adverse events during the 6 month period.

N = 35 patients

Medical and Health Uses of MLR

Table 2. Suggested Doses, Current and Potential Uses of Oral MLR Supplements

Use	Subjects/patients	Age group	MLR Lipid Supplement	NTFL Dose[a] range (g/day)	Reference
General health	Aged	senior	NTFactor/L[b]	2-3	Ellithorpe et al. [36]
Fatigue	Aged	senior	NTFactor/L	2-3	Agadjanyan et al. [37]
Fatigue	CFS/ME	adult/teen	NTFactor/L	2-4	Nicolson & Ellithorpe [38]
Fatigue	CFS/ME	adult	ATP Fuel	4	Nicolson et al. [23,41]
Fatigue	Fibromyalgia	adult	NTFactor/L	3-4	Nicolson & Ellithorpe [38]
Weight loss	Obesity, fatigue	adult	NTFactor	1-3	Ellithrope et al. [39]
General health	Neurodegenerative Dis.	adult	NTFactor/L	3-4	Nicolson et al. [46]
CD health	CD risk/CD disease	adult	NTFactor/L	2-4	Ellithorpe et al. [36]
Metabolic health	MetSyn/diabetes	adult	NTFactor/L	2-4	Nicolson [47]
Metabolic health	Diabetes	adult	ATP Fuel	4	Nicolson et al. [23]
Neurobehavior	Autism Spectrum Dis.	child	NTFactor/L	1-2	Nicolson et al. [46]
Infections	Lyme/mycoplasma	adult	ATP Fuel	4	Nicolson et al. [42]
Fertility	Fertility Diseases	adult	NTFactor/L	2-3	-
Fatigue	Cancer	adult	NTFactor/L	2-3	Nicolson and Conklin [44]
Anemia	Anemia	adult	NTFactor/L	1-2	Ellithorpe et al. [36]
Injury	Spinal injury	adult	NTFactor/L	1-2	Ellithorpe et al. [36]
Autoimmune	Rheumatoid arthritis	adult	ATP Fuel	4	Nicolson et al. [23]
General health	Pregnancy	adult	NTFactor/L	1-2	Ellithorpe et al. [36]
Chemical detox	GW Illnesses	adult	NTFactor/L	>4	Nicolson et al. [48]
Mental clarity	Aging	adult	NTFactor L	1-2	Ellithorpe et al. [49]

[a]Dose range in grams per day based on weight of NTFactor Lipids®

[b]NTFactor® or NTFactor Lipids®

CD – cardiovascular disease; CFS/ME – chronic fatigue syndrome/myalgic encephalomyelitis;
GW – Gulf War; MetSyn – metabolic syndrome;

Membrane Lipid Replacement Therapy

- MLR decreased fatigue in aged subjects, fatiguing illness patients, cancer and chronic infections (Lyme, Mycoplasma).
- MLR increased mitochondrial function in aged subjects and fatiguing illness patients (CFS, Fibromyalgia, GWI).
- MLR improved homocyteine, fasting insulin, SED, CRP
- MLR decreased deletions in mtDNA in aged subjects.
- MLR decreased adverse effects of Cancer cytotoxic therapy.
- MLR reduced other symptoms: cognitive, pain, GI symptoms.
- MLR was well tolerated (no adverse or side effects).
- Over **40 million doses** of MLR given without any adverse effects.

Lecture Summary

- Chronic infections are commonly found in various chronic medical conditions
- Chronic infections damage cellular membranes primarily by oxidizing membrane glycerolphospholipids
- Membrane integrity is linked to mitochondrial function and is characterized by loss of inner membrane potential and reduction of ATP production, causing fatigue and other symptoms. This can be reversed with Membrane Lipid Replacement.
- CFS and CFS/FM patients benefited from Membrane Lipid Replacement in terms of reduction in symptoms, including fatigue and peripheral pain.
- Membrane Lipid Replacement slowly reduces Homocysteine levels. Fasting Insulin levels, Erythrocyte SED, etc. associated with increased risk for Cardiovascular Disease and damage to the microcirculation.