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# A Simple and Safe Method to Slowly Remove Hydrophobic Aliphatic Hydrocarbons from Petrochemically Exposed Patients using a Membrane Lipid Replacement Natural Oral Supplement

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**Abstract**
Exposures to aliphatic hydrocarbons and polycyclic aromatic hydrocarbons and their heat-generated fragments during the Persian Gulf War in 1991 resulted in long-term symptoms of chemical contamination in deployed armed forces. Some of the veterans display to this day a variety of signs and symptoms related to such exposures. With our success in using oral Membrane Lipid Replacement (MLR) therapy to repair and enhance mitochondrial function and slowly remove oxidized, amphipathic lipids from cellular stores we undertook a study to see if chemically exposed veterans of the Gulf War could benefit from MLR in terms of slowly resolving various chronic signs and symptoms. After 6 months on 6 grams per day oral MLR glycerophospholipids veterans with chemical exposures showed significant reductions in signs and symptoms related to fatigue, pain, chemical sensitivities, neurologic symptoms, gastrointestinal symptoms, breathing, skin lesions and other signs and symptoms. Reductions in the severities of signs and symptoms were gradual and varied among the male subjects in this study. There were also no adverse events during the study. We propose that MLR with protected membrane glycerophospholipids is a simple and safe method to detoxify petrochemical and other hydrophobic toxic chemicals in patients with chronic signs and symptoms.

**Key Word and Phrases**
Petroleum Exposures, Environmental Health Effects, Membrane Structure, Membrane Lipid Replacement, Membrane Phospholipids, AHs Aliphatic Hydrocarbons, FMM Fluid–Mosaic Membrane, GPL, Glycerophospholipids, MLR Membrane Lipid Replacement, PAHs Polycyclic Aromatic Hydrocarbons.

## 1. Exposures to Petrochemicals and other Toxicants and their Potential Health Effects

Environmental exposures to flammable aliphatic hydrocarbons (AHs), polycyclic aromatic hydrocarbons (PAHs) and aromatic hydrocarbons (ArHs) have become a world - wide environmental and health problem [1]-[3]. When mixtures of volatile petrochemicals are incinerated, the resulting combustion gases and particles contain a wide variety of airborne materials. This includes degraded hydrocarbons (including AHs, ArHs, PAHs, others) plus additional volatile organic compounds, such as aldehydes, ketones, polynuclear aromatic compounds, among others, as well as metals, other suspended particulate matter, carbon dioxide, carbon monoxide, sulfur dioxide and other gases [4]-[5].

These released materials can become persistent hazardous pollutants in the ecosystem and cause tenacious chronic health problems in exposed populations because of their toxicity. They can also produce carcinogenic, immunotoxic and teratogenic effects [1]-[2].

Animal and human exposures to unburned and burned petrochemicals can result in multiple injuries to tissues and organs [3],[6]. Among the most difficult health problems reported are chronic symptoms related to neurotoxic and pulmonary damage that result in persistent chronic symptoms [3],[6]-[9]. In war veterans and in certain other occupations exposures to persistent airborne toxicants have placed them at high risk for neurological disorders and other chronic illnesses[9]-[11].

## 2. The Exposures of Gulf War Veterans to Petrochemical and other Chemical Toxicants

In the 1991 Gulf War military service members were exposed to multiple toxic materials from desert environments, petrochemical exhaust from military vehicles and aircraft, emissions from open-air burn pits, burning oil well fires and other chemical toxicants, including direct contact with petrochemicals and pesticides as well as receiving various toxins from multiple vaccines and prophylactic treatment with cholinergic inhibitors [9],[12]-[15]. These exposures, especially the chemical exposures, were never adequately identified or treated, and many veterans of the 1991 Gulf War have remained chronically ill to this day with multiple system and organ symptoms related to numerous toxic exposures [12]-[15]. Importantly, some of the hydrophobic environmental chemical toxicants and their burned products were likely absorbed by pulmonary and skin exposures and eventually transported and partitioned into hydrophobic structures within cells and tissues where they remained for long periods of time [15]-[18]. The presence of these chemical toxicants can slowly produce cellular damage that can result in multiple symptoms that have been related to chronic chemical exposures [15]-[18].

Using a daily oral intake schedule of protected dietary glycerophospholipids (GPL) we have developed a simple method of gradual partitioning/removal of hydrophobic chemical toxicants buried deeply inside cellular lipid structures. The ingested, amphipathic dietary GPL are efficiently absorbed by the small intestine and transported to the liver via the portal vein and then re-transported to organs, tissues and cells where they are incorporated into a variety of cellular lipid structures [17]-[19]. These cellular lipid structures include every type of intracellular membrane and various lipid carriers and lipid storage structures, such as lipid globules, lipid droplets, liposomes, chylomicrons, and other lipid-containing structures [19]. The transfer of newly absorbed dietary GPL inside cells occurs mainly by direct contact and partitioning of the lipids from internalized plasma membranes to intracellular membranes and to various intracellular lipid structures, and these replacement processes and the reverse removal processes are all driven by mass action or bulk flow mechanisms. The end result is the eventual replacement/removal of damaged cellular GPL and other lipids (usually damaged by oxidative free radicals) with undamaged GPL/lipids in various cellular membranes and other intracellular lipid structures (Membrane Lipid Replacement or MLR) [16],[17]. The process of MLR can result in the repair of vital intracellular structures like various intracellular membranes and restoration of normal cellular functions, along with the removal of damaged lipids and other lipid-sequestered molecules. Thus, excess MLR GPL can segregate deeply embedded hydrophobic toxicants, which are then sequestered and transported within the MLR lipid carriers to the plasma cell membrane and expelled from cells by an exocytotic process. Once in the extracellular medium, the MLR lipids and bound, intercalated hydrophobic toxicants are returned by a reverse passive transport process to the gastrointestinal system for bulk elimination in the stool [17]-[19]. This is how the MLR mass action or bulk flow process can slowly deplete, replace and remove hydrophobic contaminants from cells and tissues.

## 3. The Structure of Biological Membranes and its Importance in Partitioning of Intracellular Lipids and Hydrophobic Chemicals

As briefly described above, various cells have several types of lipid structures that can absorb toxic hydrocarbon molecules, and these structures can store hydrophobic toxicants for long periods of time where they can interfere with normal membrane physiologic processes. But with the help of MLR and its mass action replacement mechanism, the excess membrane GPL can eventually partition, package and remove toxic chemicals. The most common of these cellular lipid structures are the various plasma and intracellular membranes, but there are also lipid globules, lipid droplets, chylomicrons, liposomes, and other lipid structures that are important [19]. These assorted membranes and lipid structures inside cells are unique in their compositions, organizations, dynamics and functions; however, there are some general structural and other

properties that govern their organization and dynamics [20]-[22].

Since 1972 biological membranes have been described by the Fluid–Mosaic Membrane (FMM) model, which has become accepted as the basic structural model and most suitable nanometer-scale portrayal of biological membranes [20]. The FMM model was introduced in order to provide a simplified, general framework for explaining the structures and dynamics and interactions of cellular and intracellular membranes [20].

Although periodic updating of the FMM model has occurred as new data became available [21]-[25], its basic concepts have remained useful for describing the various properties of cellular membranes [24]-[25]. In addition, the relationship of biological membranes to the structures and properties of hydrophobic petrochemical compounds are important in understanding the abilities of cellular membranes to partition hydrophobic chemicals within their structures by the process of hydrophobic matching and encapsulation. This makes intracellular membranes as well as some of the other lipid structures inside cells uniquely accessible for MLR partitioning and for the mass action removal of hydrophobic chemicals, including damaged membrane lipids and other cellular lipid components from cells and tissues [16]-[19].

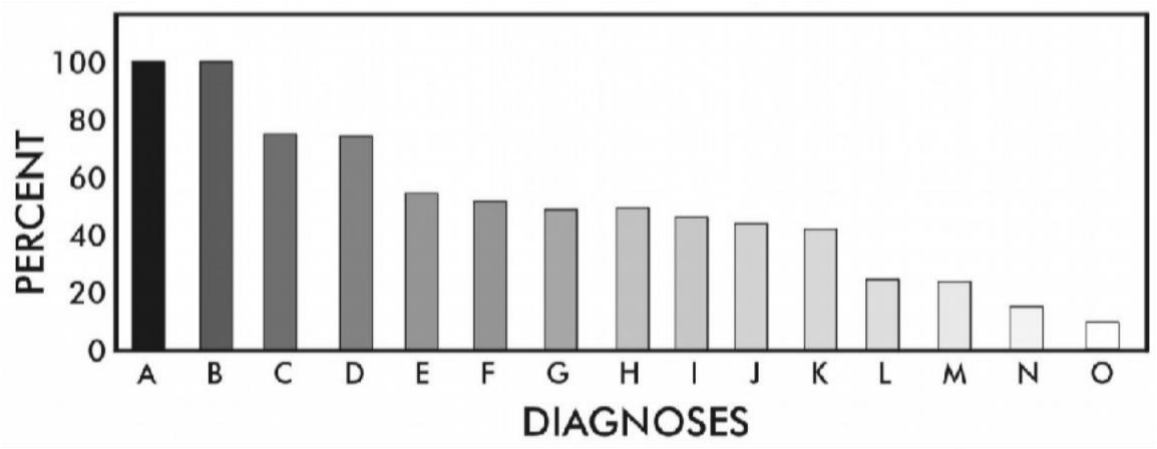


**Fig. 1** Study participants presented with various diagnoses and symptoms after the 1991 Gulf War. All participants had multiple symptoms or diagnoses before entering the trial. Percent of participants with: (**A**) Gulf War illnesses, (**B**) chronic fatigue syndrome, (**C**) multiple chemical sensitivity syndrome, (**D**) weight gain/loss, (**E**) irritable bowel syndrome, (**F**) fibromyalgia syndrome, (**G**) allergies, (**H**) skin rashes, (**I**) depression, (**J**) joint pain, (**K**) hypertension, (**L**) reactive airway symptoms, (**M**) sleep disturbances, (**N**) skin lesions, (**O**) contact dermatitis.

## 4. The Use of Membrane Lipid Replacement to Treat Chemically Exposed Patients

By combining MLR plant-derived GPL with fructooligosaccahrides to protect the orally delivered dietary phospholipids from disruption, degradation and oxidation in the storage and delivery process along with antioxidants to protect against oxidative damage we have developed several useful and safe oral MLR supplements [16]-[18]. These natural supplements have been proven to be effective in reducing disease-associated symptoms and age-associated loss of function [16]-[19].

MLR has proven useful for organ, tissue and cell membrane support, and it is especially useful for restoring mitochondrial and other essential cellular and organ functions [16]-[19], [22]-[24].

Recently, we have used protected MLR GPL to sequester and remove cellular hydrophobic toxicants and reduce symptom severities in petrochemically-exposed patients. For example, clinical case reports had suggested the usefulness of MLR in lowering some symptom severities in chemically exposed patients [26]. We subsequently demonstrated the usefulness of oral MLR GPL in treating chemically exposed Gulf War veterans and reducing their symptom severities [27].

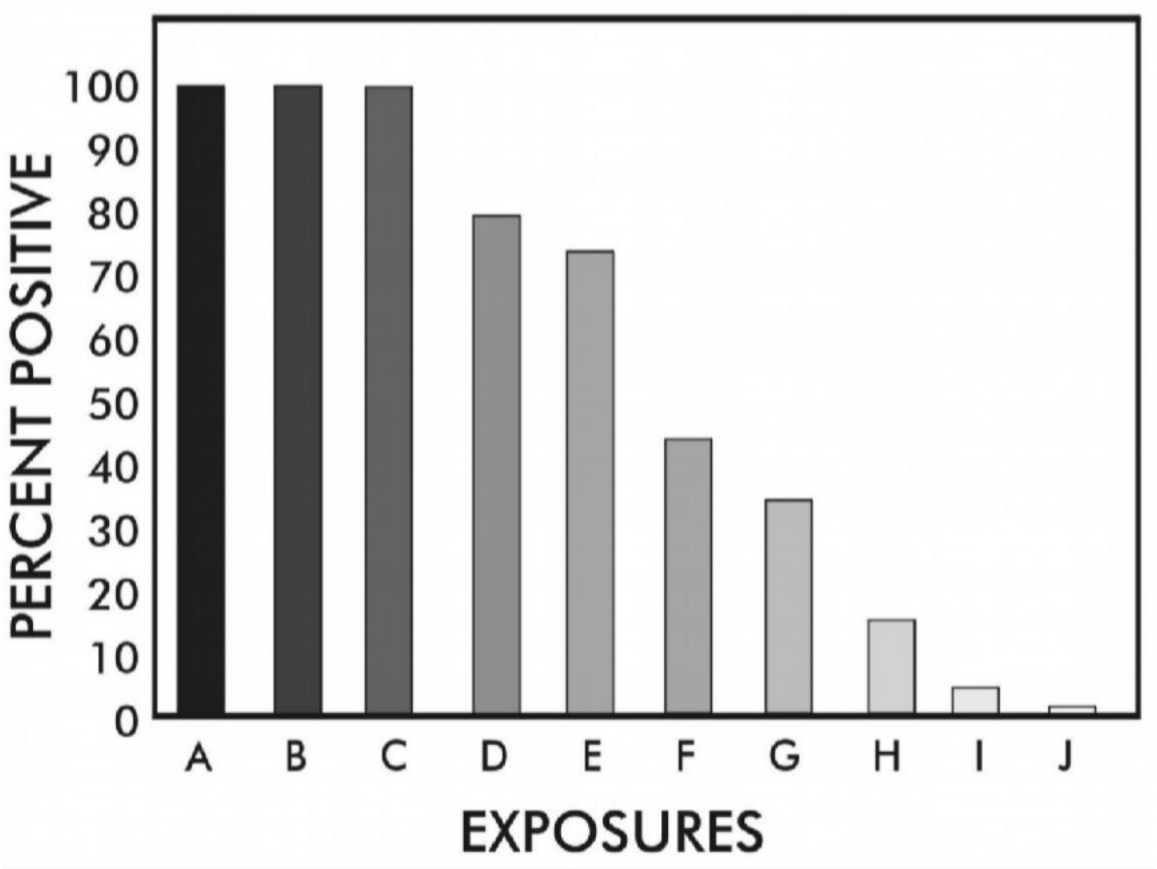


**Fig. 2** Study participants reported multiple toxic exposures during the 1991 Gulf War. Percent of trial participants exposed to: (**A**) Petroleum fuel and/or petroleum products, (**B**) Smoke from burning oil wells, (**C**) Smoke from burn pits, (**D**) Ingestion of pyridostigmine bromide, (**E**) Exposure to pesticides, (**F**) Exposure to raw sewage, (**G**) Exposure to insects, (**H**) Direct contact with dead bodies, (**I**) Presumed exposure to chemical warfare agents, and (**J**) Exposure to herbicides.

## 5. Chemically Exposed Gulf War Veterans and MLR.

Twenty male veterans that served in combat zones in Kuwait and Iraq in 1991 and have remained ill since their service were recruited for a pilot MLR study [27]. All were diagnosed with long-term multi-symptom chronic illnesses with moderate to severe signs and symptoms [27],[28]. These signs and symptoms were consistent with the most commonly used criteria for the diagnosis of Gulf War Illnesses [29]. In addition to Gulf War Illnesses, most of the veterans in the study had additional diagnoses [27]. The most common were chronic fatigue syndrome, multiple chemical sensitivity syndrome and fibromyalgia (Fig. 1). All of the participants in the study were chronically exposed to petroleum fuel, oil well fumes, smoke and burned oil, smoke from burn pits, and other exposures, and all were administered military vaccines. However, there were variable exposures to other toxic materials, including pyridostigmine bromide, pesticides, herbicides, raw sewage, dead bodies, and chemical warfare agents (Fig. 2) [27].

An open-label, Institutional Review Board-approved, clinical study was initiated to study the effects of a MLR GPL chewable wafer supplement (Patented Energy® with NTFactor® Lipids) on the severities of >100 signs and symptoms found in Gulf War Illness patients [27],[28]. This test supplement is a patented, proprietary membrane lipid preparation containing plant polyunsaturated GPL (phosphatidylcholine, phosphatidyl- glyerol, phosphatidylserine, phosphatidylinositol, and other glycerophospholipids) plus plant fructooligosaccahrides and antioxidants to protect the

phospholipids from disruption, degradation and oxidation [16],[17].

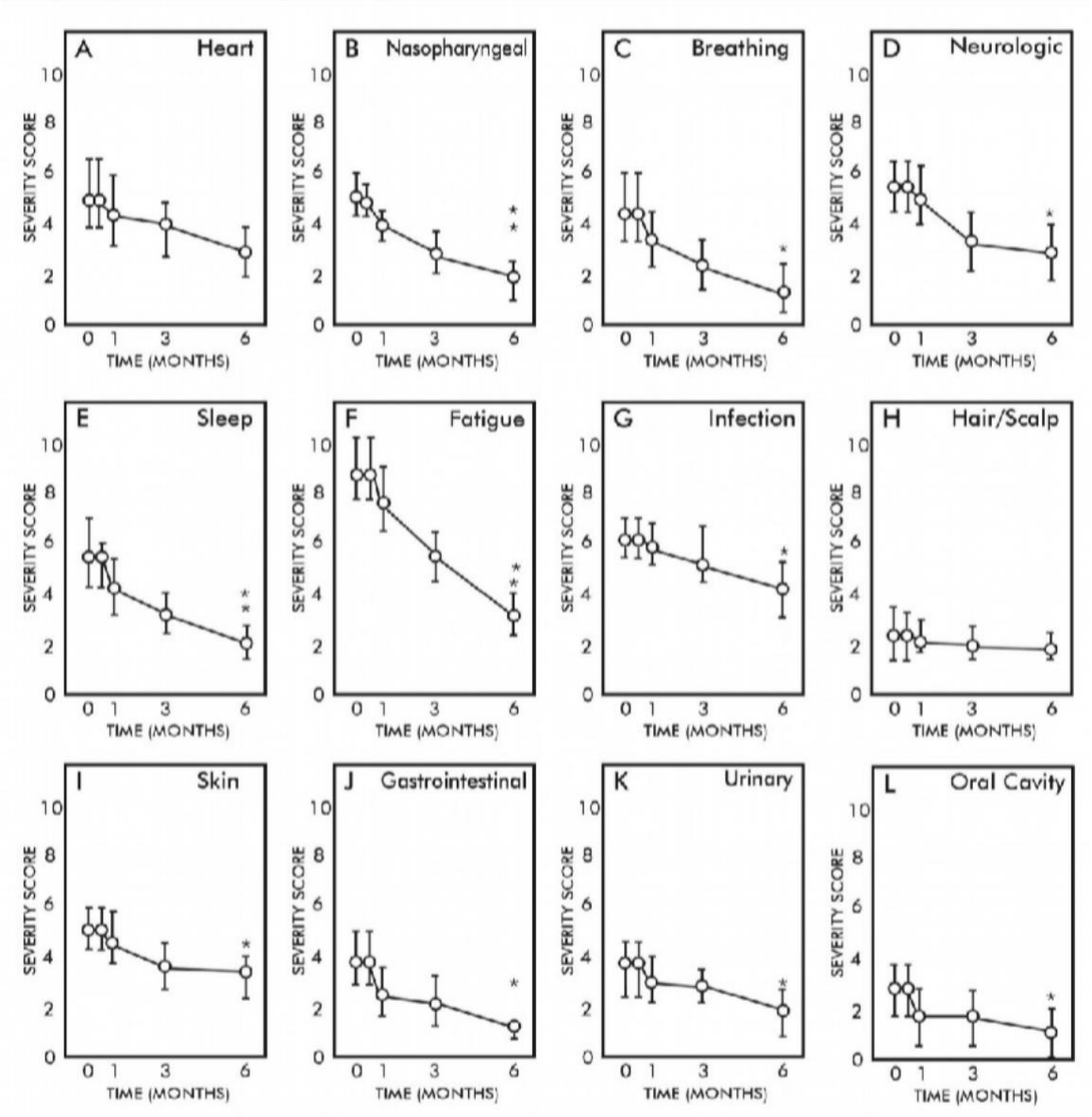


**Fig. 3 (A-L).** Self-reported symptom category scores over the time course of the clinical study. The mean symptom category severity scores (±standard deviations) of trial participants before the start of the study and at one week, one month, 3 months and 6 months of oral MLR supplement NTFactor® Lipids. (**A**) Heart symptoms, (**B**) Nasopharyngeal symptoms, (**C**) Breathing difficulties, (**D**) Neurologic symptoms, (**E**) Sleep disturbances, (**F**) Fatigue, (**G**) Infection(s), (**H**) Hair/scalp disturbances, (**I**) Skin disturbances, (**J**) Gastrointestinal symptoms, (**K**) Urinary symptoms, (**L**) Oral cavity disturbances, (*, $p<0.01$; **, $p<0.001$).

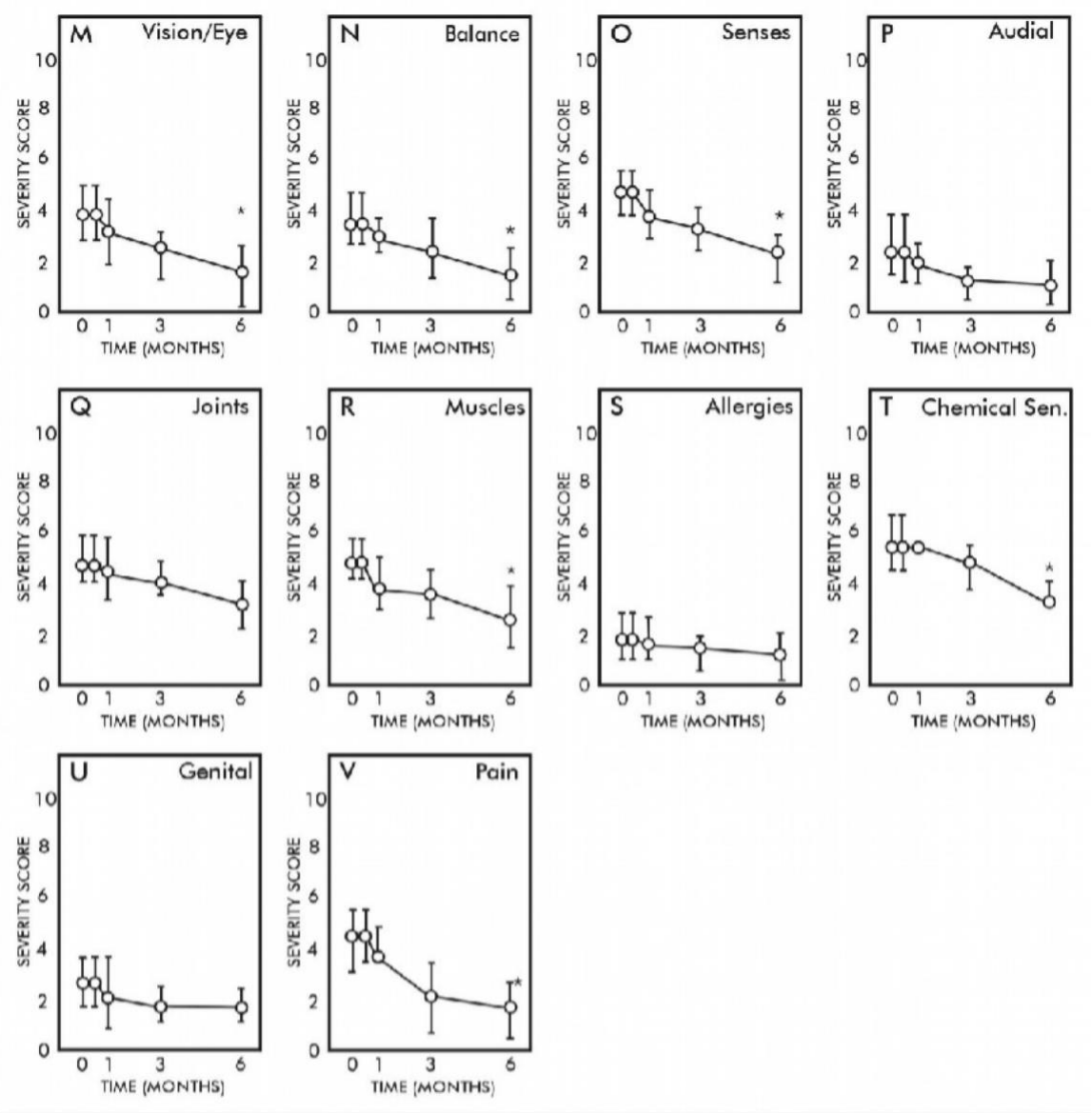


**Fig. 4 (M-V).** Self-reported symptom category scores over the time course of the clinical study. The mean symptom category severity scores (±standard deviations) of trial participants before the start of the study and at one week, one month, 3 months and 6 months of oral MLR supplement NTFactor® Lipids. (**M**) Vision/eye disturbances, (**N**) Balance disturbances, (**O**) Sense disturbances, (**P**) Audial disturbances, (**Q**) Joint symptoms, (**R**) Muscle symptoms, (**S**) Allergies, (**T**) Chemical sensitivities, (**U**) Genital disturbances, and (**V**) Pain. (*, $p<0.01$; **, $p<0.001$).

The study participants ingested 6 g/day of the oral test supplement for 6 months, and their signs and symptoms were self-reported at various times (0, 0.25, 1, 3 and 6 months) using a validated patient symptom survey form [29]. Symptom severities in the survey form were scored numerically based on a linear scale from 0 to 10 or lowest (0) to highest (10) severity of symptoms. To analyze the data from 120 signs and symptoms the individual scores were merged into 22 symptom categories to more easily assess the effects of the supplement on major organs and systems [27],[28]. Statistical analyses were performed on all clinical data by analysis of variance (ANOVA), with significance defined as $p<0.01$ or better.

## 6. Results of the MLR Clinical Study on Chemically Exposed Veterans

The chemically exposed Gulf War veterans in the MLR clinical study completed their 6-month trial of MLR phospholipids and reported differences in the symptom (category) severities and responses to the MLR test supplement (Figs. 3 and 4) [27].

Analysis of the group mean data indicated that there were gradual and significant responses to the MLR test supplement. For example, over the 6-month trial there were significant reductions in symptom severities related to fatigue, pain, musculoskeletal, nasopharyngeal, breathing, vision, sleep, balance, gastrointestinal system, chemical sensitivities and other symptom categories. The reductions that occurred were generally gradual but different in each patient in degree and over time. For example, some symptom categories, such as sleep disfunction (Fig. 3E), fatigue (Fig. 3F), gastrointestinal symptoms (Fig. 3J), chemical sensitivities (Fig. 4T), pain (Fig. 4V) and other symptoms, showed significant reductions in severities by the end of the study, but others exhibited less significant or hardly any reductions (for example, Figs. 3H, 4S, 4U) [27].

## 7. Implications of the Clinical Study on MLR Treatment of Gulf War Illnesses

Even with no apparent, single cause or definitive diagnostic criteria for diagnosing Gulf War Illnesses, there are treatment approaches that can reduce the severities of some of the signs and symptoms of this condition [12],[14],[26],[27]. Most of the treatments for Gulf War veterans have been developed based on toxic chemical or radiological exposures encountered during deployment, problems with military vaccines, or in the use of counter-measures to presumed exposure to offensive chemical warfare agents [9],[12]-[15]. Various treatments to address specific exposures, such as infections, chemical exposures and neurotoxicants, depleted uranium, physical trauma, stress, and other treatments have been undertaken in various clinical studies with mixed results [9],[12],[13],[26]-[28].

Other treatment approaches for Gulf War Illness patients have been based on individual patients' functional decrements or changes. For example, in one study mitochondrial function in Gulf War Illness patients was shown to be reduced by examining post-exercise phosphocreatine recovery time [29]. Often reductions in the mitochondrial cofactor coenzyme Q10 ($CoQ_{10}$) have been associated with loss of mitochondrial function [30], and this information was used to design a clinical study that supplemented patients with $CoQ_{10}$ [31]. Several different natural supplements have been used to boost mitochondrial dysfunction, depending on the specific lesion in ingredient transport, electron transport chain dysfunction or other defects [32],[33]. MLR phospholipids have also been used to successfully treat mitochondrial dysfunction due to inner mitochondrial membrane damage, such as the trial supplement used here (NTFactor® Lipids) that repairs the inner mitochondrial membrane and restores mitochondrial inner membrane trans-membrane electrical-chemical potential necessary for function and ATP production [34].

The success of the MLR natural oral supplement treatment regimen used here and in other studies suggested that MLR with protected membrane GPL could be a useful approach for other types of petrochemical exposures that result in chronic signs and symptoms similar to those reported here [1]-[15]. An important point to emphasize is that MLR with oral GPL is completely safe and innocuous, and the U.S. Food and Drug Administration has determined that the MLR glycerophospholipids are "generally regarded as safe" (GRAS) [35].

MLR natural supplements like NTFactor® Lipids have been successfully used in a variety of chronic health conditions, such as those associated with aging and age-related illnesses, and especially those with symptoms like fatigue, pain and other symptoms [36]. In addition, these same supplements have been used to reduce the adverse effects of therapy in cancer and infectious diseases [37].

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## Conflicts of Interest

G.L.N. is a part-time consultant to Nutritional Therapeutics, Inc. of New York and Naturally Plus, Inc. of Taiwan. No other possible conflicts of interest are reported.

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