



## Membrane Lipid Replacement—a functional approach to repairing cellular membranes, reducing symptoms, and restoring function

Garth L. Nicolson

Department of Molecular Pathology, The Institute for Molecular Medicine, Huntington Beach, California, USA

**Corresponding Author:** Professor Emeritus Garth L. Nicolson, PhD, MD (H), The Institute for Molecular Medicine, P.O. Box 9355, S. Laguna Beach, CA 92652 USA

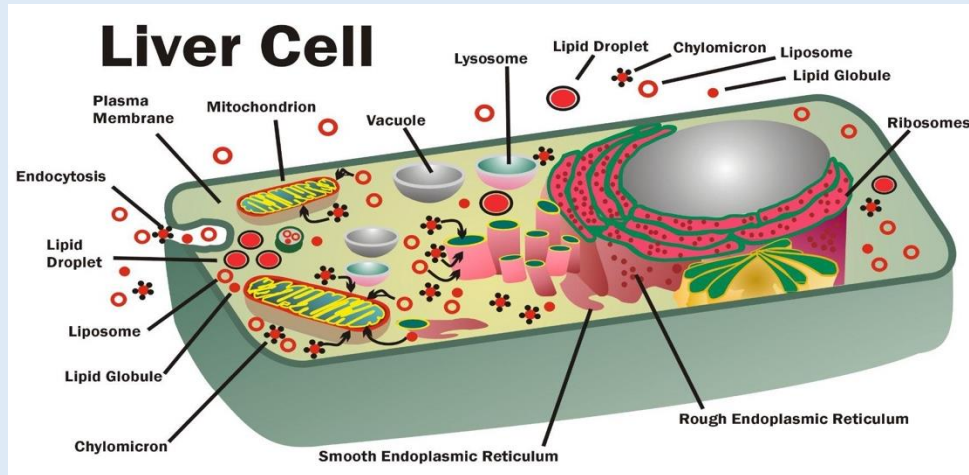
**Submission Date:** August 13, 2022; **Acceptance date:** August 30th, 2022; **Publication date:** August 31<sup>st</sup>, 2022

**Please cite this article as:** Nicolson G. L. Membrane Lipid Replacement—a functional approach to repairing cellular membranes, reducing symptoms, and restoring function. *Functional Food Science*. 2022; 2(8): 198-204. DOI: 10.31989/ffs.v2i8.990

### ABSTRACT

Membrane Lipid Replacement (MLR) uses natural, protected membrane lipid supplements to safely replace damaged, oxidized lipids in cellular membranes in order to restore membrane function, decrease various symptoms and improve health. Membrane injury occurs in essentially all chronic and acute medical conditions as well as in normal aging and development. The repair of damaged cellular membranes, and the removal of impaired membrane lipids and other toxic molecules from cells, are essential to recovery and health. Clinical studies have demonstrated the advantages of MLR in restoring membrane and organelle function and reducing fatigue, pain and other symptoms in chronic illnesses and aging patients. MLR has also been used in in vitro studies to demonstrate its ability to increase cell motility and resistance to oxidative damage. It also has the ability to enhance the bioavailability of other nutrients and their transport across intestinal epithelial cell barriers.

**Keywords:** membrane phospholipids, lipid transport, lipid oxidation, mitochondrial function, fatigue, pain, chronic disease symptoms, aging



©FFC 2022. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0>)

## INTRODUCTION

Membrane Lipid Replacement (MLR), the use of all-natural, protected, plant-sourced oral membrane lipid supplements to safely replace damaged, oxidized lipids in cellular membranes, can restore membrane and organelle function, decrease chronic symptoms, and improve health outcomes [1-5]. MLR supplements fit the definition of functional foods and contain mixtures of cell membrane glycerolphospholipids, fatty acids, and other lipids that are protected by fructooligosaccharides and antioxidants [1-3]. Once ingested, the MLR phospholipids are transported to tissues and cells where these MLR lipids can replace and remove damaged intracellular and cellular membrane lipids as well as other hydrophobic toxic molecules from cells and tissues [3,5,6].

Membrane injury, caused mainly by free radical oxidative damage, occurs in essentially all chronic and acute medical conditions, including cancers, degenerative diseases, environmental exposures, and in

normal processes, such as aging and development [4-7]. After ingestion, the protected MLR glycerolphospholipids and other lipids are dispersed, absorbed, and internalized in the small intestines, where they can be subsequently transferred, exchanged or partitioned into circulating lipoproteins, liposomes, micelles, and membranes of circulating cells and other lipid carriers. They are then transported in the lymphatics and blood circulation to tissue and cellular sites where they are taken in by cells using various transport mechanisms. Once inside cells, the MLR glycerolphospholipids and other lipids are conveyed by concentration-dependent partitioning into various intracellular membranes mediated by lipid carriers, lipid globules, liposomes, chylomicrons, or by direct intracellular membrane-membrane interactions [2,3,5]. The entire process appears to be driven by 'bulk flow' or 'mass action' principles, where surplus concentrations of replacement lipids can stimulate the natural exchange and removal of damaged membrane lipids. The replacement lipids can

undergo further enzymatic alterations at their ultimate cellular membrane sites to reflect the lipid compositions at these sites [2,5,8].

## CLINICAL STUDIES

Human studies have demonstrated the advantages of MLR in restoring membrane and organelle function, reducing fatigue, pain, and other symptoms in chronic illness and aging [1-7]. For example, the use of MLR supplementation to improve age-related symptoms in middle-aged, pre- and post-menopausal women was investigated in a randomized, double-blind, placebo-controlled study [9]. The study subjects, post-menopausal women, complained of fatigue but were otherwise relatively healthy. The participants in this clinical trial were given MLR with NTFactor Lipids or placebo for 4 or 8 weeks, and fatigue, vigor, mood, and various menopause symptoms were monitored. The women that received 1.2 g per day NTFactor Lipids showed greater reductions in fatigue compared to placebo, and there were significant improvements in patient vigor. Sleep, confusion, anger, and menopausal symptoms were evaluated using Quality of Life instruments and showed improvements in the MLR group. Cardiovascular parameters were also examined, and in the MLR group there were reductions in diastolic blood pressure and improvements in cardio-ankle vascular index [9].

A recent use of MLR in environmental illnesses was initiated for chemically exposed war veterans [6,10]. Many veterans of the first Gulf War returned and slowly displayed multiple signs and symptoms related to their

deployment and environmental exposures. The multi-symptom chronic illnesses associated with this war have been called Gulf War Illness(es) (GWI) [11,12]. Some GWI patients appear to have their illnesses linked to chemical exposures, such as oil spills and fires, smoke from military operations, chemicals on clothing, and exposures to pesticides, chemoprophylactic agents (pyridostigmine bromide), chemical weapons, and other possible chemicals [13,14].

We first initiated case studies on veterans of the Gulf War that reported a variety of signs and symptoms that were related to their chemical exposures. These case studies indicated that MLR could improve clinical status by reducing symptoms, such as fatigue, pain, and other symptoms [10]. Next, a clinical study was initiated using oral NTFactor Lipids (6 g per day) to see if veterans' self-reported multiple symptom severities improved with time while on the oral MLR supplement. In this study there were gradual and significant reductions in symptom severities related to fatigue, pain, musculoskeletal, nasopharyngeal, breathing, vision, sleep, balance, gastrointestinal symptoms, chemical sensitivities, and other symptom categories during the 6-month study [6].

Other examples of the use of MLR in various health and clinical conditions are listed in Table 1. What is notable about the potential uses of MLR in humans is that these conditions span multiple situations, from common conditions like obesity and aging to various degenerative and metabolic diseases and cancers. What is clear from these studies is that MLR can also be a useful addition to conventional medical treatments for a number of

commonly found illnesses and conditions to repair the severities of a variety of chronic signs and symptoms  
 damaged cellular membranes and in the process reduce as well improve general health [1-5].

**Table 1.** Current and potential uses of oral MLR supplements and revised suggested daily dose levels.<sup>a</sup>

Use/condition	Subjects/patients	Age	MLR type	NTFL dose <sup>b</sup>	Example
		Group	Supplement	Range (g/day)	Reference(s)
General health	aged	senior	NTFactor/L <sup>c</sup>	2-3	Nicolson et al. [4]
Fatigue	Aged	senior	NTFactor/L	4	Agadjanyan et al. [15]
Fatigue	CFS/ME	adult/teen	NTFactor/L	4	Nicolson & Ellithorpe [16]
Fatigue	CFS/ME	adult	ATP Fuel	4	Nicolson et al. [17]
Inflammation	Chronic fatigue	adult	ATP360	N/A <sup>d</sup>	Hamilton & Jensen [18]
Fatigue	Fibromyalgia	adult	NTFactor/L	4	Nicolson et al. [19]
Fatigue	Menopause	senior	NTFactor/L	2	Hirose et al. [9]
Weight loss	Obesity, fatigue	adult	NTFactor	2	Ellithorpe et al. [20]
Brain health	Neurodegen. dis	adult	NTFactor/L	4	Nicolson et al. [21]
CD health	CD risk/CD dis.	adult	NTFactor/L	3-4	Ellithorpe et al. [22]
Metabolic health	MetSyn/diabetes	adult	NTFactor/L	3-4	Nicolson [23]
Metabolic health	Diabetes	adult	ATP Fuel	3-4	Nicolson et al. [17]
Neurobehavior	Autism Spectrum dis.	child	NTFactor/L	1-3	Nicolson et al. [3]
Infections	Lyme/mycoplasma	adult	ATP Fuel	4	Nicolson et al. [24]
Fertility	Fertility Diseases	adult	NTFactor/L	3-4	Ferreira et al. [25]
Fatigue	Cancer	adult	NTFactor/L	3-4	Nicolson [26]
Anemia	Anemia	adult	NTFactor/L	3-4	Nicolson et al. [3]
Injury	Spinal injury	adult	NTFactor/L	3-4	Ellithorpe et al. [12,123]
Autoimmune	Rheumatoid arthritis	adult	ATP Fuel	4	Nicolson et al. [12,123]
General health	Pregnancy	adult	NTFactor/L	2-3	Ellithorpe et al. [27]
Chemical detox	GW Illnesses	adult	NTFactor/L	6	Nicolson & Breeding [6,10]

<sup>a</sup>Modified from Nicolson et al. [5]. Abbreviations: CD, cardiovascular disease; CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis; GW, Gulf War; MetSyn, metabolic disease/syndrome; MLR, Membrane Lipid Replacement; N/A, not applicable; NTFL, NTFactor Lipids;

<sup>b</sup>Suggested revised dose range in grams per day based on NTFactor Lipids<sup>®</sup>

<sup>c</sup>NTFactor<sup>®</sup> or NTFactor Lipids<sup>®</sup>

<sup>d</sup>Not Available

## OTHER STUDIES

MLR lipids have been used to demonstrate the role of membrane integrity in maintaining cellular function. For example, NTFactor Lipids® can repair mitochondrial membranes and restore mitochondrial function in human cells [15]. MLR has also been used to repair spermatozoa membranes and increase the motility of sperm and resistance to oxidative damage [25,28].

Finally, MLR can improve the transport and bioavailability of nutrients not associated with MLR ingredients. Using an intestinal epithelial bioabsorption tissue culture model based on the transport of nutrients across a monolayer of human intestinal Caco-2 cells, NTFactor Lipids® was found to increase the transport and bioavailability of three test nutrients (coenzyme Q10, curcumin and quercetin) [29]. Therefore, in addition to its own abilities to improve health outcomes, MLR has the potential to improve the bioavailability and properties of various other nutrients that could also be beneficial to health [29].

## CONCLUSION

Clinical trials have shown the efficacy and usefulness of MLR supplements in reducing symptoms associated with loss of mitochondrial and other cellular functions and improving the quality of life in patients with a variety of chronic illnesses and normal age-related loss of function. Recent efforts have focused on the effects of MLR supplements on reducing pain, gastrointestinal and other symptoms as well as age-related functional loss. MLR can also improve the bioavailability of certain nutrients and improve membrane function and cellular properties, such as cell motility [25,28].

**List of Abbreviations:** GWI, Gulf War Illnesses; MLR, Membrane Lipid Replacement

**Author's Contribution:** The author is responsible for all aspects of this contribution.

**Competing Interests:** The author is a part-time consultant to Nutritional Therapeutics, Inc. of New York, NY and Naturally Plus Taiwan, Inc. of Taipei, Taiwan.

**Acknowledgments and Funding:** Financial support was provided by the Institute for Molecular Medicine and Nutritional Therapeutics, Inc. I thank John Michael for graphic assistance.

**Patient Consent:** All patients mentioned in this contribution consented to use their clinical information via informed consent documents. All data collection and patient evaluations were approved by independent institutional review boards.

## REFERENCES

1. Nicolson GL. Membrane Lipid Replacement: Clinical studies using a natural medicine approach to restoring membrane function and improving health. Intern J Clin Med 2016; 7: 133-143. DOI: [10.4236/ijcm.2016.72015](https://doi.org/10.4236/ijcm.2016.72015)
2. Nicolson GL, Ash ME. Membrane Lipid Replacement for chronic illnesses, aging and cancer using oral glycerolphospholipid formulations with fructooligosaccharides to restore phospholipid function in cellular membranes, organelles, cells and tissues. Biochim Biophys Acta Biomembr 2017; 1859: 1704-1724. DOI: [10.1016/j.bbame.2017.04.013](https://doi.org/10.1016/j.bbame.2017.04.013)
3. Nicolson GL, Rosenblatt S, Ferreira de Mattos G, Settineri R, Breeding PC, Ellithorpe RR, Ash ME. Clinical uses of Membrane Lipid Replacement supplements in restoring membrane function and reducing fatigue in chronic diseases and cancer. Discoveries 2016; 4(1): 54. DOI: [10.15190/d.2016.1](https://doi.org/10.15190/d.2016.1)
4. Nicolson GL, Breeding PC, Settineri R, Ferreira de Mattos G. Aging and chronic illnesses: Membrane Lipid Replacement for restoring mitochondrial function and reducing fatigue, pain, and other symptoms in aged individuals. Bioact Comp Health Dis 2020; 3(10): 194-203. DOI: [10.31989/bchd.v3i10.749](https://doi.org/10.31989/bchd.v3i10.749)
5. Nicolson GL, Ferreira de Mattos G, Ash M, Settineri R, Escribá PV. Fundamentals of Membrane Lipid Replacement, a natural medicine approach to reducing fatigue, pain, and other symptoms while restoring function in chronic illnesses and aging. Membranes 2021;11(12): 944. DOI: [10.3390/membranes11120944](https://doi.org/10.3390/membranes11120944)

6. Nicolson GL, Breeding PC. Membrane Lipid Replacement with glycerolphospholipids slowly reduces self-reported symptom severities in chemically exposed Gulf War veterans. *Intern J Transl Med* 2022; 2(2): 164-173. DOI: [10.3390/ijtm2020014](https://doi.org/10.3390/ijtm2020014)
7. Nicolson GL, Settineri R. Lipid Replacement Therapy: a functional food approach with new formulations for reducing cellular oxidative damage, cancer-associated fatigue and the adverse effects of cancer therapy. *Funct Foods Health Dis* 2011; 1(4): 135-160. DOI: [10.31989/ffhd.v1i4.134](https://doi.org/10.31989/ffhd.v1i4.134)
8. Mayor S, Presley JF, Maxfield FR. Sorting of membrane components from endosomes and subsequent recycling to the cell surface occurs by a bulk flow process. *J Cell Biol* 1993; 121: 1257–1269. DOI: [10.1083/jcb.121.6.1257](https://doi.org/10.1083/jcb.121.6.1257)
9. Hirose A, Terauchi M, Osaka Y, Akiyoshi M, Kato K, Miyasaka N. Effect of soy lecithin on fatigue and menopausal symptoms in middle-aged women: a randomized, double-blind, placebo-controlled study. *Nutrit J* 2018; 17: article 4. DOI: [10.1186/s12937-018-0314-5](https://doi.org/10.1186/s12937-018-0314-5)
10. Nicolson GL, Breeding PC. Membrane Lipid Replacement for reduction of pain, fatigue, gastrointestinal and other symptoms in patients with peripheral pain: case reports. *Case Rep Rev* 2020; 1(2): 1-3. DOI: [10.33425/2693-1516.1007](https://doi.org/10.33425/2693-1516.1007)
11. Nicolson GL, Nicolson NL. Chronic fatigue illnesses and Operation Desert Storm. *J Occup Environ Med* 1996; 38: 14-16. DOI: [10.1097/00043764-199601000-00003](https://doi.org/10.1097/00043764-199601000-00003)
12. Kang, HK. Mahan CM, Lee KY, Magee CA, Murphy FM. Illnesses among United States veterans of the Gulf War: a population-based survey of 30,000 veterans. *J Occup Environ Med* 2000; 42: 491-501 DOI: [10.1097/00043764-200005000-00006](https://doi.org/10.1097/00043764-200005000-00006)
13. Nicolson GL, Berns P, Nasralla M, Haier J, Nicolson NL, Nass M. Gulf War Illnesses: chemical, radiological and biological exposures resulting in chronic fatiguing illnesses can be identified and treated. *J Chronic Fatigue Syndr* 2003; 11(1): 135-154. DOI: [10.1300/J092v11n01\\_04](https://doi.org/10.1300/J092v11n01_04)
14. White RF, Steele L, O'Callaghan PP, Sullivan K, Binns JH, Golomb BA, Bloom FE, Bunker JA, Crawford F, Graves JC, Hardie A, Klimas N, Knox M, Meggs WJ, Melling J, Philbert MA, Grashow R. Recent research on Gulf War Illness and other health problems in veterans of the 1991 Gulf War: effects of toxicant exposures during deployment. *Cortex* 2016; 74: 449-475. DOI: [10.1016/j.cortex.2015.08.022](https://doi.org/10.1016/j.cortex.2015.08.022)
15. Agadjanyan M, Vasilevko V, Ghochikyan A, Berns P, Kesslak P, Settineri RA, Nicolson GL. Nutritional supplement (NTFactor) restores mitochondrial function and reduces moderately severe fatigue in aged subjects. *J Chronic Fatigue Syndr* 2003; 11(3): 23-36. DOI: [10.1300/J092v11n03\\_03](https://doi.org/10.1300/J092v11n03_03)
16. Nicolson GL, Ellithorpe R. Lipid replacement and antioxidant nutritional therapy for restoring mitochondrial function and reducing fatigue in chronic fatigue syndrome and other fatiguing illnesses. *J Chronic Fatigue Syndr* 2006; 13(1): 57-68. DOI: [10.1300/J092v13n01\\_06](https://doi.org/10.1300/J092v13n01_06)
17. Nicolson GL, Settineri R, Ellithorpe E. Lipid Replacement Therapy with a glycerolphospholipid formulation with NADH and CoQ10 significantly reduces fatigue in intractable chronic fatiguing illnesses and chronic Lyme disease. *Intern J Clin Med* 2012; 3(3): 164-170. DOI: [10.4236/ijcm.2012.33034](https://doi.org/10.4236/ijcm.2012.33034)
18. Hamilton D, Jensen GS. Nutraceutical support of mitochondrial function associated with reduction of long-term fatigue and inflammation. *Altern Ther* 2021; 27: 8-18. <https://pubmed.ncbi.nlm.nih.gov/33882028/>
19. Nicolson GL, Settineri R, Ferreira G, Breeding P. Reduction of pain, fatigue, gastrointestinal and other symptoms and improvement in quality of life indicators in fibromyalgia patients with Membrane Lipid Replacement glycerolphospholipids and controlled-release caffeine. *Intern J Clin Med* 2018; 9: 560-579. DOI: [10.4236/ijcm.2018.97051](https://doi.org/10.4236/ijcm.2018.97051)
20. Ellithorpe RA, Settineri R, Jacques B, Nicolson GL. Lipid Replacement Therapy functional food with NT Factor for reducing weight, girth, body mass, appetite, cravings for foods and fatigue while improving blood lipid profiles. *Funct Foods Health Dis* 2012; 2(1): 11-24. DOI: [10.31989/ffhd.v2i1.102](https://doi.org/10.31989/ffhd.v2i1.102)
21. Nicolson GL, Settineri R, Ellithorpe R. Neurodegenerative and fatiguing illnesses, infections and mitochondrial dysfunction: use of natural supplements to restore mitochondrial function. *Funct Foods Health Dis* 2014; 4(1): 23-65. DOI: [10.31989/ffhd.v4i1.26](https://doi.org/10.31989/ffhd.v4i1.26)
22. Ellithorpe RR, Settineri R, Ellithorpe T, Nicolson GL. Blood homocysteine and fasting insulin levels are reduced and erythrocyte sedimentation rates are increased with a glycerolphospholipid-vitamin formulation: a retrospective study in older subjects. *Funct Foods Health Dis* 2015; 5(4): 126-135. DOI: [10.31989/ffhd.v5i4.177](https://doi.org/10.31989/ffhd.v5i4.177)
23. Nicolson GL. Metabolic syndrome and mitochondrial function: molecular replacement and antioxidant supplements to prevent membrane oxidation and restore mitochondrial function. *J Cell Biochem* 2007; 100(6): 1352-1369. DOI: [10.1002/jcb.21247](https://doi.org/10.1002/jcb.21247)

24. Nicolson GL, Settineri R, Ellithorpe E. Glycophospholipid formulation with NADH and CoQ10 significantly reduces intractable fatigue in chronic Lyme disease patients: preliminary report. *Funct Foods Health Dis* 2012; 2(3): 35-47. DOI: [10.31989/ffhd.v2i3.100](https://doi.org/10.31989/ffhd.v2i3.100)
25. Ferreira G, Costa C, Bassaizteguy V, Santos M, Cardozo R, Montes J, Settineri R, Nicolson GL. Incubation of human sperm with micelles made from glycerolphospholipid mixtures increases sperm motility and resistance to oxidative stress. *PLoS One* 2018; 13(6): e0197897. DOI: [10.1371/journal.pone.0197897](https://doi.org/10.1371/journal.pone.0197897)
26. Nicolson GL. Lipid replacement therapy: a nutraceutical approach for reducing cancer-associated fatigue and the adverse effects of cancer therapy while restoring mitochondrial function. *Cancer Metastasis Rev* 2010; 29(3): 543-552. DOI: [10.1007/s10555-010-9245-0](https://doi.org/10.1007/s10555-010-9245-0)
27. Ellithorpe RR, Settineri R, Nicolson GL. Reduction of fatigue by use of a dietary supplement containing glycophospholipids. *J Am Nutraceut Assoc* 2003; 6(1): 23-28.
28. Medica AJ, Aitkin RJ, Nicolson GL, Sheridan AR, Swegan A, De Luliis G, Gib Z. Glycerophospholipids protect stallion spermatozoa from oxidative damage in vitro. *Reprod Fertil* 2021; 2: 199-209. DOI: [10.1530/RAF-21-0028](https://doi.org/10.1530/RAF-21-0028)
29. Settineri R, Ji J, Shields ZP, Shirvani T, McLaren CE, Nicolson GL. The effects of Membrane Lipid Replacement with NTFactor® Lipids on increasing the bioavailability of three test nutrients. *Bioact Comp Health Dis* 2022; 5(5): 106-116. DOI: [10.31989/bchd.v5i5.936](https://doi.org/10.31989/bchd.v5i5.936)