

# Finally an Answer to the Most Common Medical Complaint – Fatigue

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\*The author has no financial interest in the products discussed in this contribution.

## Abstract

*The most common complaint of patients seeking general medical assistance is fatigue. Fatigue occurs naturally during aging and in most degenerative diseases, including neurological, respiratory, coronary, musculoskeletal, metabolic and gastrointestinal diseases as well as infections and cancer, and it is characterized at the cellular level by diminished mitochondrial function through loss of efficiency in the electron transport chain. Lipid Replacement Therapy administered using an all-natural nutritional supplement containing membrane glycopospholipids and antioxidants can reduce or prevent fatigue and membrane oxidative damage and restore mitochondrial function. Recent clinical trials using patients with chronic fatigue have shown the benefit of Lipid Replacement Therapy in restoring mitochondrial electron transport function and reducing moderate to severe chronic fatigue.*

## Introduction

Chronic or intractable fatigue that is not reversed by sleep is the most common complaint of patients seeking medical care.<sup>1,2</sup> It is also an important secondary condition in many degenerative diseases and occurs naturally during aging.<sup>1</sup> The phenomenon of fatigue has been defined as a multidimensional sensation, and clinical studies have determined the extent of fatigue in various medical conditions and its possible causes.<sup>3-5</sup> Many diseases are associated with fatigue, including neurological, respiratory, coronary, musculoskeletal, metabolic and gastrointestinal diseases as well as infections and cancer.<sup>2-7</sup>

Most patients understand fatigue as a loss of overall energy and inability to perform even simple tasks without exertion. At the cellular level fatigue is related to cellular energy systems found primarily in the cells' mitochondria. Damage to mitochondrial components, especially mitochondrial membranes, occurs mainly by oxidation, and this can result in increased ion leakage across mitochondrial membranes and impair the ability of mitochondria to produce high-energy molecules needed for survival and growth.<sup>8</sup> During aging and most chronic diseases the production of oxidative molecules, such as Reactive Oxygen and Nitrogen species (ROS/RNS), can cause oxidative stress and cellular damage, resulting in oxidation of lipids, proteins and DNA.<sup>9-11</sup> When oxidized, these molecules are structurally and sometimes functionally changed. Important targets of ROS/RNS damage are mitochondria, mainly their phospholipid-containing membranes, as well as cellular and mitochondrial DNA.<sup>9-11</sup>

One of the most important changes in tissues and cells during aging and in chronic degenerative diseases is accumulated oxidative damage due to ROS/RNS. ROS/RNS are oxidative and free radical oxygen- and nitrogen-containing molecules, such as nitric oxide, oxygen and hydroxide radicals and other molecules.<sup>9</sup> Critical targets of these cellular oxidants are the genetic apparatus and cellular membranes,<sup>8,9</sup> and in the case of cellular membranes oxidation can affect lipid fluidity, permeability and membrane function.<sup>12,13</sup> Similar damage occurs in fatiguing illnesses, such as chronic fatigue syndrome (CFS), where patients have intractable fatigue for at least six months and show increased susceptibility to oxidative stress and peroxidation.<sup>14,15</sup>

<sup>1</sup> Kroenke K, Wood DR, Mangelsdorff AD, et al. Chronic fatigue in primary care. Prevalence, patient characteristics, and outcome. *JAMA* 1988; 260:929-934. <sup>2</sup> Morrison JD. Fatigue as a presenting complaint in family practice. *J Family Pract* 1980; 10:795-801. <sup>3</sup> McDonald E, David AS, Pelosi AJ, Mann AH. Chronic fatigue in primary care attendees. *Psychol Med* 1993; 23:987-998. <sup>4</sup> Piper BF, Dribble SL, Dodd MJ, et al. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncol Nursing Forum* 1998; 25:667-684. <sup>5</sup> Piper BF, Linsey AM, Dodd MJ. Fatigue mechanism in cancer. *Oncol Nursing Forum* 1987; 14:17-23. <sup>6</sup> Nicolson GL. Lipid replacement as an adjunct to therapy for chronic fatigue, anti-aging and restoration of mitochondrial function. *J Am Nutraceut Assoc* 2003; 6(3):22-28. <sup>7</sup> Nicolson, G.L. and Ellithrope, 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. <sup>8</sup> Kanno T, Sato EE, Muranaka S, Fujita H, Fujiwara T, Utsumi T, Inoue M, Utsumi K. Oxidative stress underlies the mechanism for Ca(2+)-induced permeability transition of mitochondria. *Free Radical Res* 2004; 38(1):27-35. <sup>9</sup> Huang H, Manton KG. The role of oxidative damage in mitochondria during aging: a review. *Front Biosci* 2004; 9:1100-1117. <sup>10</sup> Richter C, Par JW, Ames B. Normal oxidative damage to mitochondrial and nuclear DNA is extensive. *Proc Nat Acad Sci USA* 1998; 85:6465-6467. <sup>11</sup> Wei YH, Lee HC. Oxidative stress, mitochondrial DNA mutation and impairment of antioxidant enzymes in aging. *Exp Biol Med* 2002; 227:671-682. <sup>12</sup> Nicolson GL, Poste G, Ji T. Dynamic aspects of cell membrane organization. *Cell Surface Rev* 1977; 3:1-73. <sup>13</sup> Subczynski WK, Wisniewska A. Physical properties of lipid bilayer membranes: relevance to membrane biological functions. *Acta Biochim Pol* 2000; 47:613-625. <sup>14</sup> Logan AC, Wong C. Chronic fatigue syndrome: oxidative stress and dietary modifications. *Altern Med Rev* 2001; 6(5): 450-459. <sup>15</sup> Manuel y Keenoy B, Moorckens G, Vertommen J, De leeuw I. Antioxidant status and lipoprotein peroxidation in chronic fatigue syndrome. *Life Sci* 2001; 68:2037-2049.

In this brief review I will concentrate on recent clinical trials that have shown the effectiveness of lipid replacement therapy (LRT) plus antioxidants in the treatment of certain clinical disorders and conditions, such as chronic fatigue.<sup>6,7</sup> LRT is not just the dietary substitution of certain lipids with proposed health benefits; it is the actual replacement of damaged cellular lipids with undamaged (unoxidized) lipids to ensure proper function of cellular structures, mainly cellular and organelle membranes.<sup>6,7</sup> During LRT lipids must be protected from oxidative and other damage, and this is also necessary during storage as well as during ingestion, digestion, and absorption *in vivo*.<sup>6</sup> LRT must result in the cellular delivery of unoxidized, undamaged membrane glycopospholipids in order to replace damaged lipids and restore function to oxidized cellular membranes. Combined with antioxidant supplements, LTR has proven to be an effective method to prevent ROS/RNS-associated changes in cellular activities and functions and for use in the treatment of various clinical conditions.<sup>7</sup>

### Lipid Supplements and Health Benefits

Dietary supplements made up of mixtures of lipids have been used to improve general health.<sup>16,17</sup> They have also been used as adjunct treatments in various clinical conditions. For example, n-3 fatty acids have been used in the adjunct treatment of cardiovascular diseases and inflammatory disorders.<sup>17-20</sup> Most studies have documented the value of dietary lipid supplements that favor certain types of lipids, such as n-3 polyunsaturated fatty acids (mainly fish- or flaxseed-derived) relative to n-6 lipids.<sup>16-20</sup> However, not every clinical study has found health benefits from lipid dietary supplementation.<sup>21</sup>

Lipid replacement is possible because in the body cellular lipids are in dynamic equilibrium.<sup>6</sup> Orally ingested

lipids diffuse to the gut epithelium and are bound and eventually transported into the blood and lymph using specific carrier alipoproteins and also by nonspecific partitioning and diffusion mechanisms.<sup>22,23</sup> Within minutes, lipid molecules are transported from gut to endothelial cells, then excreted into and transported in the blood circulation bound to lipoproteins and blood cells where they are generally protected from oxidation.<sup>22,23</sup> Once in the circulation, specific lipoprotein carriers and red blood cells protect lipids throughout their passage and eventual deposition onto specific cell membrane receptors where they can be taken into cells via endosomes and by diffusion.<sup>24,25</sup> After binding to specific cell surface receptors that bring the lipids into cells, lipid transporters in the cytoplasm deliver specific lipids to cell organelles where they are taken in by specific transport, partitioning, and diffusion.<sup>26</sup> The concentration gradients that exist from the gut to the tissues are important in driving lipids into cells. Similarly, damaged lipids are removed by a similar reverse process that may be driven by lipid transfer proteins and by enzymes that recognize and degrade damaged lipids.<sup>6,26</sup>

### Oxidative Damage to Mitochondria and Chronic Fatigue

Excess ROS/RNS production can result in lifetime accumulation of mitochondrial and nuclear oxidative damage.<sup>9-11</sup> On the other hand, cellular free-radical scavenging enzymes neutralize excess ROS/RNS and repair the enzymes that reverse oxidation-mediated damage.<sup>11</sup> Although some ROS/RNS production is important in triggering cell proliferation, gene expression and destruction of invading microbes,<sup>28,29</sup> with aging oxidative damage accumulates.<sup>9-11,27</sup> When this occurs, antioxidant enzymes and enzyme repair mechanisms along with biosynthesis cannot restore or replace enough damaged molecules.<sup>9-11,29-31</sup>

<sup>6</sup> Nicolson GL. Lipid replacement as an adjunct to therapy for chronic fatigue, anti-aging and restoration of mitochondrial function. *J Am Nutraceut Assoc* 2003; 6(3):22-28. <sup>7</sup> Nicolson, G.L. and Ellithrope, 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. <sup>8</sup> Kanno T, Sato EE, Muranaka S, Fujita H, Fujiwara T, Utsumi T, Inoue M, Utsumi K. Oxidative stress underlies the mechanism for Ca(2+)-induced permeability transition of mitochondria. *Free Radical Res* 2004; 38(1):27-35. <sup>9</sup> Huang H, Manton KG. The role of oxidative damage in mitochondria during aging: a review. *Front Biosci* 2004; 9:1100-1117. <sup>10</sup> Richter C, Par JW, Ames B. Normal oxidative damage to mitochondrial and nuclear DNA is extensive. *Proc Nat Acad Sci USA* 1998; 85:6465-6467. <sup>11</sup> Wei YH, Lee HC. Oxidative stress, mitochondrial DNA mutation and impairment of antioxidant enzymes in aging. *Exp Biol Med* 2002; 227:671-682. <sup>12</sup> Nicolson GL, Poste G, Ji T. Dynamic aspects of cell membrane organization. *Cell Surface Rev* 1977; 3:1-73. <sup>13</sup> Subczynski WK, Wisniewska A. Physical properties of lipid bilayer membranes: relevance to membrane biological functions. *Acta Biochim Pol* 2000; 47:613-625. <sup>14</sup> Logan AC, Wong C. Chronic fatigue syndrome: oxidative stress and dietary modifications. *Altern Med Rev* 2001; 6(5): 450-459. <sup>15</sup> Manuel y Keenoy B, Moorkens G, Vertommen J, De leeuw I. Antioxidant status and lipoprotein peroxidation in chronic fatigue syndrome. *Life Sci* 2001; 68:2037-2049. <sup>16</sup> Harris WS. n-3 fatty acids and lipoproteins: comparison of results from human and animal studies. *Lipids* 1996; 31:243-252. <sup>17</sup> Connor WE. Importance of n-3 fatty acids in health and disease. *Am J Clin Nutr* 2000; 71:S171-S178. <sup>18</sup> Butcher G, Hengstler HC, Schindler P, Meier C. n-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med* 2002; 112:298-304. <sup>19</sup> Belluzzi A. n-3 fatty acids for the treatment of inflammatory bowel diseases. *Proc Nutr Soc* 2002; 61:391-393. <sup>20</sup> Calder PC. Dietary modification of inflammation with lipids. *Proc Nutr Soc* 2002; 61:345-358. <sup>21</sup> Grimble RF. Nutritional modulation of immune function. *Proc Nutr Soc* 2001; 60:389-397. <sup>22</sup> Hajri T, Abumrad NA. Fatty acid transport across membranes: relevance to nutrition and metabolic pathology. *Annu Rev Nutr* 2002; 22:383-415. <sup>23</sup> Hamilton JA. Fatty acid transport: difficult or easy? *J Lipid Res* 1998; 39(3):467-481. <sup>24</sup> Fellmann P, Herve P, Pomorski T, Muller P, et al. Transmembrane movement of diether phospholipids in human erythrocytes and human fibroblasts. *Biochem* 2000; 39:4994-5003. <sup>25</sup> Conner SD, Schmid SL. Regulated portals of entry into the cell. *Nature* 2003; 422:37-44. <sup>26</sup> Mansbach CM, Dowell R. Effect of increasing lipid loads on the ability of the endoplasmic reticulum to transport lipid to the Golgi. *J Lipid Res* 2000; 41:605-612. <sup>27</sup> Harman D. Aging: A theory based on free radical and radiation chemistry. *J Gerontol* 1956; 2:298-300. <sup>28</sup> Halliwell B. Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. *Drugs Aging* 2001; 18:685-716. <sup>29</sup> Tan, NSS, Vinckenbosch NS, Liu N, Yasmin P, Desvergne R, et al. Selective cooperation between fatty acid binding proteins and peroxisome proliferator-activated receptors in regulating transcription. *Mol Cell Biol* 2002; 22:5114-51127. <sup>30</sup> Chen D, Cao G, Hastings T et al. Age-dependent decline of DNA repair activity for oxidative lesions in rat brain mitochondria. *J Neurochem* 2002; 81:1273-1284. <sup>31</sup> Xu D, Finkel T. A role for mitochondria as potential regulators of cellular life span. *Biochem Biophysics Res Commun* 2002; 294:245-248.

Disease and infection can result in excess oxidative damage that exceeds the abilities of cellular systems to repair and replace damaged molecules,<sup>10, 15, 28</sup> and this also occurs in fatiguing illnesses, such as Fibromyalgia Syndrome and CFS.<sup>14, 15</sup> In CFS patients there is evidence of oxidative damage to DNA and lipids,<sup>14, 15, 32</sup> as well as the presence of blood markers that are indicative of excess oxidative stress.<sup>33</sup> CFS patients also have sustained elevated levels of the RNS molecule peroxynitrite due to excess nitric oxide, and this results in lipid peroxidation and loss of mitochondrial function as well as changes in cytokine levels that exert a positive feedback on nitric oxide production.<sup>34</sup> In addition to mitochondrial membranes, mitochondrial enzymes are also inactivated by peroxynitrite, and this could also contribute to loss of mitochondrial function.<sup>35</sup><sup>36</sup> In addition, cellular molecules that could counteract the excess oxidative capacity of ROS/RNS, such as glutathione and cysteine, have been found in lower levels in CFS patients.<sup>37</sup>

### Antioxidants Help Prevent Oxidative Damage

Preventing oxidative damage of cellular and mitochondrial membranes and DNA are important in preventing loss of cellular energy.<sup>6, 14, 31, 38</sup> This can be accomplished, in part, by neutralizing ROS/RNS with various antioxidants or increasing free-radical scavenging systems that neutralize ROS/RNS. Thus dietary antioxidants and some accessory molecules, such as zinc and certain vitamins, are important in maintaining antioxidant and free-radical scavenging systems.<sup>14</sup> In addition to zinc and vitamins, there are at least 40 micronutrients required in the human diet,<sup>39</sup> and aging increases their need to prevent age-associated damage to mitochondria and other cellular elements. Antioxidant use alone, however, may not be sufficient to maintain cellular components free of ROS/RNS damage, and it cannot reverse the damage once it occurs. Thus, LRT is necessary to replace oxidation-damaged membrane lipids.<sup>6, 7</sup>

Dietary antioxidant supplementation has partially reversed the age-related declines in cellular antioxidants and mitochondrial enzyme activities and prevented mitochondria from most

age-associated functional decline. For example, in rodents fed diets supplemented with antioxidants the antioxidants were found to inhibit the progression of certain age-associated changes in cerebral mitochondrial electron transport chain enzyme activities.<sup>40, 41</sup> These animal studies have shown that antioxidants can partially prevent age-associated changes. However, antioxidants alone cannot completely eliminate oxidative damage to mitochondria, and this is why LRT is an important addition to antioxidant supplementation.<sup>6, 7</sup>

Dietary antioxidants can also modify the pathogenesis of certain diseases.<sup>6, 7, 14</sup> For example, antioxidant administration has been shown to have certain neuroprotective effects.<sup>42</sup> The dietary use of antioxidants has been shown to prevent age-associated mitochondrial dysfunction and damage, inhibit the age-associated decline in immune and other functions and prolong the lifespan of laboratory animals.<sup>42-44</sup>

### LRT in Preclinical and Clinical Studies

Replacing damaged cellular and mitochondrial membrane phospholipids and other lipids is an important role of lipid replacement therapy (LRT).<sup>6, 7</sup> One LRT dietary supplement is NTFactor<sup>®</sup>, which has been used successfully in animal and clinical lipid replacement studies.<sup>45</sup><sup>46</sup> Its encapsulated lipids are protected from oxidation in the gut and can be absorbed and transported into tissues without oxidative damage. This dietary supplement contains a variety of components, including phospholipids, glycopospholipids and other lipids, nutrients, probiotics, vitamins, minerals and plant extracts.<sup>6</sup>

In animal studies this LRT supplement has been used to prevent hearing loss associated with aging.<sup>47</sup> Seidman et al.<sup>47</sup> found that this LRT supplement prevented hearing loss associated with aging and shifted the threshold hearing from 35-40 dB in control aged animals to 13-17 dB in the treatment group (P<0.005). They also found that it preserved cochlear mitochondrial function, increasing mitochondrial function by 34%. It also prevented aging-related mitochondrial DNA deletions found in the cochlear.<sup>47</sup>

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LRT has also been successfully used in clinical studies to reduce fatigue and protect cellular and mitochondrial membranes from oxidative damage.<sup>45, 46</sup> For example, this dietary supplement has been used in a vitamin and mineral mixture in cancer patients to reduce the effects of cancer therapy, such as chemotherapy-induced fatigue, nausea, vomiting and other side effects associated with chemotherapy.<sup>48</sup> This double-blinded, cross-over, placebo-controlled, randomized trial on cancer patients receiving chemotherapy showed that LRT improved fatigue, nausea, diarrhea, impaired taste, constipation, insomnia and other quality of life indicators.<sup>48</sup>

NTFactor<sup>®</sup> has been used in a study with severely chronic fatigued patients to reduce their fatigue.<sup>45</sup> Using the Piper Fatigue Scale<sup>5</sup> we found that fatigue was reduced approximately 40.5% (P<0.0001), from severe to moderate fatigue, after eight weeks of LRT supplementation with NTFactor<sup>®</sup>.<sup>45</sup> Recently we examined the effects of this form of lipid replacement therapy on fatigue in moderately and mildly fatigued subjects and to determine if their mitochondrial function improved.<sup>46</sup> Use of this LRP dietary supplement<sup>®</sup> for 8 or 12 weeks resulted in a 33% or 35.5% reduction in fatigue, respectively (P<0.001).<sup>46</sup> In this clinical trial there was good correspondence between reductions in fatigue and gains in mitochondrial function.

After only 8 weeks of LRT, mitochondrial function was significantly improved (P<0.001), and after 12 weeks LRT supplementation, mitochondrial function was found to be similar to that of young healthy adults.<sup>46</sup> After 12 weeks of supplement use, subjects discontinued the supplement for an additional 12 weeks, and their fatigue and mitochondrial function were again measured. After the 12-week wash-out period, fatigue and mitochondrial function were intermediate between the initial starting values and those found after eight or 12 weeks on supplement, indicating that continued dietary LTR is probably required to show improvements in mitochondrial function and maintain lower fatigue scores.<sup>46</sup> The results indicate that in moderately to severely fatigued subjects dietary LRT can significantly improve and even restore mitochondrial function and significantly improve fatigue. Similar results were found with CFS and/or Fibromyalgia Syndrome patients indicating that LRT plus antioxidants for 8 weeks reduced moderate to severe fatigue by 43.1%.<sup>7</sup> 🌸

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<sup>5</sup> Piper BF, Linsey AM, Dodd MJ. Fatigue mechanism in cancer. *Oncol Nursing Forum* 1987; 14:17-23. <sup>7</sup> Nicolson, G.L. and 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. <sup>45</sup> Ellithorpe RR, Settineri R, Nicolson GL. Pilot Study: Reduction of fatigue by use of a dietary supplement containing glycopospholipids. *J Am Nutraceut Assoc* 2003; 6(1):23-28. <sup>46</sup> Agadjanyan M, Vasilevko V, Ghochikyan A, Berns P, Kesslak P, Settineri R, Nicolson GL. Nutritional supplement (NTFactor) restores mitochondrial function and reduces moderately severe fatigue in aged subjects. *J Chronic Fatigue Syndr* 2003; 11(3):23-26. <sup>48</sup> Colodny L, Lynch K, Farber C, Papish S, et al. Results of a study to evaluate the use of Propax to reduce adverse effects of chemotherapy. *J Am Nutraceut Assoc* 2000; 2:17-25.