Lipid Replacement Therapy: Is it a New Approach in Patients with Chronic Fatigue Syndrome?

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Abstract: Lipid replacement therapy (LRT) is an anti-aging product which reverses age-related changes in the lipid composition of organ and tissue cells. Since membrane lipids oxidation seems to be involved in the pathogenesis of Chronic Fatigue Syndrome (CFS), their substitution with new lipids coming from dietary supplements is speculated to be effective in CFS. We have analyzed some of the most recent articles about the effects of LRT in fatigue, showing the evidences supporting this theory as well as alluding to the weak points of the studies.

Keywords: Lipid replacement therapy, Chronic Fatigue Syndrome, Reactive Oxygen Species, Mitochondrial damage, Cancer, Phosphatidylcoline.

FOREWORD

Lipid replacement therapy (LRT) is an anti-aging product invented and patented by Yechezkel Barenholz and Elishalom Yechiel in 1989 [1]. They defined it as "a method of treating a relatively aged animal to reverse age-related changes in the lipid composition of organ and tissue cells". In fact, membrane lipid composition changes in aging, with a decrease in phosphatidylcholine levels and an increase of sphingomyelin and cholesterol. These biochemical changes are accompanied by a decrease in energy production, as observed in murine myocardial cells in culture, where the aging of membrane lipid composition and the decrease of beating rate, run in parallel [2-4]. In particular, they performed an *in vivo* study [3] in which murine myocardial cells were divided into three groups. The first group was fed with phosphatidylcoline for all the duration of the study, witch lasted 20 days. During this time, the cells maintained a beating rate of 160 beats/minute. The second group was fed with a broad cultured phosphatidylcoline-free. The beating rate of cells began dropping off day after day till the 12th day, when their beating rate was only 20 beats/minute. The third group was fed with phosphatidylcoline only till the 11th day. After that time their beating rate dropped almost immediately in the same way of the second group. On the 16th day, phosphatidylcoline was added in the broad culture of the second and third group and in just 24 hours the myocardial cells started rebeating 160 beats/minute. From these amazing observations, Barenholz and Yechiel speculated that changing in lipid composition of cells may ameliorate cells' activity and energy production. Thus, they performed a preclinical study in which 18 months old rats were injected parenterally with three doses of phosphatidylcholine-rich liposomes every three days for six days. After the final administration, they found that the phosphatidylcholine/ phosphatidylserine *ratio* and the cholesterol content in red cells were completely reversed. Moreover, there was a deep decline of CPK levels in serum and heart cells, which normally increase during aging. The values were compared with those obtained from two control groups: one made of relatively young animals (three months old) and one consisting of untreated eighteen months animals. The following studies demonstrated that cellular lipids are in a dynamic equilibrium in the body [5]: in fact, in blood, lipids bound to lipoproteins and to blood cells are driven into cells thanks to the concentration gradient between the blood and the cells. In particular, lipids are exchanged with cells through passive diffusion or *via* endosomes [6, 7]. On the contrary, damaged lipids are recognised and removed by enzymes and substituted by new molecules [8]. The surprising results obtained by LRT in preventing the harmful effect of aging in cells were further confirmed by Seidman *et al*. [9]. When the researchers administered lecithin (an analogous of phosphatidylcoline) into mice, they observed that age-related hearing loss was delayed. In fact, lecithin displayed a protective role on mitochondrial damage caused by Reactive Oxygen Species (ROS), which are believed to be the culprit in the damage of cochlear

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cells. After six months of orally administration of lipids, the experimental group showed better levels of hearing sensitivities, higher mitochondrial membrane potential and lower presence of mitochondrial DNA deletions associated with aging.

LRT AND CHRONIC FATIGUE SYNDROME

Chronic Fatigue Syndrome is a debilitating disease characterized by a deep reduction of every kind of activity [10]. The persistent or recurrent fatigue lasts for more than 6 months and is often accompanied by diffuse musculoskeletal pain, sleep disturbances, and subjective cognitive impairment. Symptoms are not caused by ongoing exertion, are not relieved by rest. Biological, genetic, infectious and psychological mechanisms have been proposed, but the aetiology of CFS is not yet understood and it may have multiple causes. Nevertheless, it is now believed that oxidative stress plays an important role in CFS leading to mitochondrial dysfunction [11-14].

The amazing effects of LRT in mitochondrial function led some scientists, and in particular Nicolson *et al*., to reconsider its use in patients suffering from Chronic Fatigue Syndrome [15-24]. To prove their theory, the authors performed several clinical studies [15-20] in which they used a new product, NT Factor® (see Table **1**), as a lipid replacement therapy. In particular, in one of the trials [15], NT Factor® was administered to 20 subjects not randomly chosen and recruited using a health talk radio program. At the beginning of the study their fatigue was measured using the Piper Fatigue Scale and after the 12th week, a significant amelioration of symptoms was observed, especially in those with severe fatigue. On the contrary, fatigue started to increase again after the 24th week (12 week wash-out period) [15]. Notably, a more recent clinical study has demonstrated that the beneficial effects of NT Factor® begin within one week [16]. Nicolson *et al*. [15] also detected mitochondrial function in mononuclear cells, by evaluating transport and reduction of the dye Rhodamine-123. Rhodamine 123 is a cell-permeant, cationic, green-fluorescent dye that is readily sequestered by active mitochondria without cytotoxic effects. This product has been used to assay mitochondrial membrane potential. The staining of mitochondria with Rhodamine-123 changed significantly throughout the course of treatment with LRT. In fact, after 12 weeks of this treatment, the Rhodamine-123 mitochondrial assay yielded results similar to and not significantly different from those found in non-fatigued young adults that had not taken LRT [15]. In a following study, an amazing decrease in fatigue of 40.5% within 8 weeks was observed in 34 patients treated with antioxidants *plus* NT Factor® [17]. Moreover, NT Factor® turned out to be effective in reducing fatigue secondary to chemotherapies, as demonstrated in a double blinded cross-over placebo controlled randomized study [18]. Finally, in the last two clinical trials new different compositions of LRT were tested: NT Factor lipids® (see Table **2**) and ATP fuel® (see Table **3**). In particular, the former was administered to a volunteer group of 29 subjects with various fatigue levels who were attending an afternoon health seminar at a medical clinic. Using the Piper Fatigue Scale they observed that the overall fatigue, among participants, was reduced within the 3-hour seminar by a mean of 39.6% ($p<0.0001$) [19]. The latter was administered to 58 patients with a chart diagnosis of Chronic Fatigue Syndrome, Fibromyalgia, Gulf War Syndrome, Lyme Disease, Rheumatoid Arthritis, observing a significant decrease in fatigue in all of these subcategories within two months [20].

DISCUSSION

The idea to replace lipids damaged with peroxydation, may be effective in re-establishing the

Table 1: NT Factor® Ingredients

NT Factor®	is a nutrient complex extracted and prepared using proprietary processes. It is composed only of food and food components listed as:
Phosphoglycolipids	includes polyunsaturated phosphatidylcholine, glycolipids and other polyunsaturated phosphatidyl nutrients.
Bifido Bacterium, L. Bacillus, L. Acidophilus	freeze-dried and microencapsulated in a state of suspended animation with potential to form healthy microflora colonies.
Growth Media	Foods and bacterial growth factors to support microflora colonies including rice bran extract, arginine, beet root fiber, black strap molasses, glycine, magnesium sulfate, para-amino-benzoate, leek, pantethine (bifido growth factor), taurine, garlic, calcium borogluconate, potassium citrate, calcium sulfate, spirulina, bromelain, natural Vitamin E, calcium ascorbate, alpha-lipoic acid, oligosaccharides, B-6, niacinamide, riboflavin, inositol, niacin, calcium pantothenate, thiamin, B-12, folic acid, chromium picolinate

Table 2: NT Factor Lipids® Ingredients

NT Factor Lipids is a Patent-pending polyunsaturated, Phosphoglycolipid and nutrient blend containing:
The major phospholipids: Phosphatadic Acid(PA), phosphatidyl-Choline(PC), phosphatidyl-ethanolamine(PE), phosphatidyl-glycerol(PG), phosphatidyl-inositol(PI), and phosphatidyl-serine(PS), digalactosyldiacyglyceride(DGDG), monogalactosyldiacylglyceride (MGDG), minor phospholipids and Glycolipids extracted from soy.
Other ingredients: purified water, natural mixed berry flavor, red beet, malic acid.

Table 3: ATP Fuel® Ingredients

Vitamin (as d-alpha tocopherol)	20 IU
NT Factor Maximum Potency . . . . . **Phosphoglycolipds** - includes polyunsaturated phosphatidylcholine, glycolipids and other polyunsaturated phosphatidyl nutrients derived from soybean. **Bidido and Lactobacillus bacterium** Growth Media - foods and bacterial growth factors to support microflora colonies including rice bran extract, arginine, beet root fiber, blackstrap molasses, glycine, magnesium sulfate, para-amino-benzoate, leek, pantethine (bifido grwoth factor), taurine, garlic, calcium borogluconate, potassium citrate, calcium sulfate, spirulina, bormelain, natural Vitamin E, calcium ascorbate, alpha-lipoic acid, oligosaccharides, B-6, niacinamide, riboflavin, inositol, niacin, calcium pantothenate, thiamin, B-12, folic acid, chromium picolinate	1500 mg
Mitochondria Pro Regulator . . . . . Calcium (as phosphate/sulfate/pyruvate), Phosphorus (as calcium phosphate), Magnesium (as sulfate)	260 mg
Krebs Cycle Glucose Absorb . . . . . Alpha-Ketoglutaric Acid, L-Tyrosine	180 mg
RN Fatty Acid Metabolizer . . . . . L-Carnitine-L-Tartrate, Pantethine (as coenzyme A precursor)	140 mg
Other Ingredients Microcrystalline cellulose, croscarmellose, sodium, methyl cellulose, vegetable magnesium stearate, silica	

integrity of the mitochondrial membrane, which is necessary for the maintenance of the membrane electrical potential, therefore for energy production [15, 19, 21-24]. Thus, the increasing levels of energy in the entire body may allow hampering and decreasing fatigue.

The clinical studies managed by Nicolson *et al*. [15-20] seems to confirm his intuition, allowing to introduce in the market a new, effective, natural and free of side effects product.

The amazing effect of this new therapy in patients suffering from Chronic Fatigue Syndrome is even more important if it is considered that no pharmacologic or alternative medicine therapies have been proven effective and only cognitive behaviour therapy and graded exercise therapy seems to show moderate improvement in fatigue and other related symptoms [25].

Despite the prodigious results obtained in clinical trials, some points remain to be clarified. For instance, most of the studies were managed without a control group [15-17, 19, 20], while in those where it was done, the number of patients were limited (18). In addition, in their first clinical studies [15-18], Nicolson *et al*. administered Propax® (Table **4**) to patients. Actually, Propax® is a mixture of different components where NT factor® is mentioned as the main responsible for the beneficial results observed in patients with fatigue. Moreover, NT factor® is described in Nicolson's papers as a nutritional supplement made of different phospholipids [21]. However, as shown in Table **1**, NT factor does not contain only lipids. Indeed, it contains also vitamins, probiotics, garlic and leek [24]. They are

Table 4: Propax Ingredients

Supplement Facts		
Serving Size 1 Packet		
Servings Per Container 15 30 60 90		
Amount Per Serving		% Daily Value**
Calories	11	1%
Calories from Fat	9	†
Calories from Saturated Fat	2	†
Total Fat:	1 g	2%
Saturated Fat	0.2 g	1%
Cholesterol	1 mg	< 1%
Total Carbohydrates	0.11 g	< 1%
Sodium	0 mg	0%
Protein	0.25 g	< 1%
Vitamin A (54 % as retinyl acetate, 46% as natural beta carotene)	8,125 IU	163%
Vitamin C (as calcium ascorbate)	150mg	250%
Vitamin D3 (as cholecalciferol)	500 IU	125%
Vitamin E (as d-alpha tocopheryl succinate)	146 IU	487%
Vitamin K (as phytonadione)	2.5 mcg	3%
Thiamin (Vitamin B-1) (as thiamine HCl)	6.25 mg	417%
Riboflavin (Vitamin B-2) (as riboflavin, and riboflavin 5' phosphate)	30 mg	1765%
Niacin (Vitamin B-3) (as niacinamide, inositol hexanicotinate, niacin)	60 mg	300%
Vitamin B-6 (as pyridoxine HCl, pyridoxal 5' phosphate)	40 mg	2000%
Folate (as folic acid)	200 mcg	50%
Vitamin B-12 (as cyanocobalamin)	25 mcg	417%
Biotin	25 mcg	8%
Pantothenic acid (as d-calcium pantothenate)	25 mg	250%
Calcium (as dicalcium phosphate, caclcium citrate, calcium pyruvate, calcium ascorbate, d-calcium pantothenate, calcium borogluconate)	400 mg	40%
Phosphorus (as dicalcium phosphate)	50 mg	5%
Iodine (from kelp)	18.75 mcg	13%
Magnesium (as magnesium oxide, magnesium carbonate, magnesium glycinate)	160 mg	40%
Zinc (as zinc monomethionine)	12.5 mg	83%
Selenium (as L-selenomethionine)	75 mcg	107%
Copper (as copper glycinate)	0.3 mg	15%
Manganese (as manganese glycinate)	2.5 mg	125%
Chromium (as Chromium polynicotinate)	50 mcg	42%
Molybdenum (as molybdenum glycinate)	20 mcg	27%
Potassium (as potassium chloride, potassium citrate)	12.8 mg	< 1%
Citrus bioflavonoid complex [50% total bioflavonoids (150 mg)]	300 mg	†
L-Carnipure® L-Carnitine L-tartrate	160 mg	†
EPA (as Eicosapentaenoic Acid)	180 mg	†
DHA (as (Docosahexaneoic Acid)	120 mg	†

(Table 4). Continued.

Alpha keto glutaric acid	125 mg	†
Taurine	100 mg	†
Pantethine (a Coenzyme A Precursor)	70 mg	†
L-Tyrosine	60 mg	†
PABA	55 mg	†
Decaffeinated Green tea extract (Camellia sinensis) (dried leaves) [Standardized for 95% Polyphenols (47.5 mg), 45% Epigallocatechin-3-P-gallate (22.5 mg)]	50 mg	†
Inositol (as inositol, inositol hexanicotinate)	25 mg	†
N-Acetyl-L-Cysteine	25 mg	†
Silicon [from Horsetail extract (Equisetum arvense) (herb)]	12.5 mg	†
Grapeseed extract (Vitis vinifera) (inner core of fruit) [Standardized for 95% proanthocyanidins (4.75mg)]	5 mg	†
L-Glutathione (reduced)	5 mg	†
Quercetin (as dihydrate) (Dimorphandra gardeniaria Fam. Leguminosae) (seeds)	5 mg	†
Rose hips powder (Rosa canina) (fruit)	5 mg	†
Rutin (Sophora japonica L) (seeds)	5 mg	†
Boron (as calcium borogluconate)	500 mcg	†
Vanadium (as vanadyl sulfate)	12.5 mcg	†
NT Factor® (includes phosphoglycolipids from soy)	1560 mg	†

† Daily Value not established.
** Daily Values are based on a 2,000 calorie per day diet.
Tablet Other ingredients: Microcrystalline cellulose, vegetable stearic acid, vegetable magnesium stearate, croscarmellose sodium, and pharmaceutical glaze.
Soft Gel Other ingredients: Fish oil concentrate, gelatin, glycerin, and water.
Contains fish (anchovies, sardines, mackerel) and Soy
This product contains NO milk, egg, peanuts, crustacean shellfish (lobster, crab or shrimp), tree nuts, wheat, yeast, gluten. Contains NO artificial sweeteners, flavors, or colors.

used, according to Nicolson *et al*., to regularize the intestinal flora yielding a better absorption of the LRT through the gut [19]. However, we cannot infer whether LRT works by itself or not. In addition, Propax® was administered with some antioxidants [17], therefore, again, it is difficult to conclude whether LRT is effective by itself or not. Furthermore, in the last study, patients were treated with a new cutting-edge product, made of NADH, CoQ10 and NT factor Energy® [20]. Although NT Factor Energy® is mentioned as made of lipids only [20], careful researches allowed shedding light on its composition (Table **3**). Surprisingly, it is not made just of lipids, since vitamins, minerals and probiotics are present, too. Interestingly, in the fourth study, Nicolson *et al*. described a prodigious improvement in fatigue in just three hours using NT factor lipids® [19] (Table **2**). Despite the impressive results obtained with this energetic drink, a question comes to mind spontaneously: how does it work? How is it possible that lipids are replaced in just three hours with an improvement of energy of a mean of 39.6%? Further studies have to be performed in order to confirm the clinical study and to understand the mechanism behind this phenomenon. Finally, Piper Fatigue Scale (PFS) was used to choose subjects with fatigue and to divide them into those with mild, moderate and severe symptoms. The PFS is routinely used by medical researchers to scientifically measure fatigue levels in patients during clinical studies [26]. The 22 question PFS enable to quickly and accurately assess the current level of fatigue. Originally developed to measure fatigue in cancer patients, the PFS has been successfully used in a variety of medical areas for over 20 years now. The PFS in its current form is composed of 22 numerically scaled, "0" to "10" items that measure four dimensions of subjective fatigue: behavioural/severity (6 items); affective meaning (5 items); sensory (5 items); and cognitive/mood (6 items). These 22 items are used to calculate the four sub-scale/dimensional scores and the total fatigue scores. Thus, PFS is not a diagnostic scale for patients suffering from CFS: it is a questionnaire to determinate the subjective feeling of fatigue. Therefore, the clinical studies mentioned before, demonstrated that Propax®,

NT factor & Co® are effective in subjects with fatigue, and not in those with a diagnosis of CFS. However, since LRT is a nutritional supplement and not a drug, it is not subjected to the same severe supervision of health regulating authorities, such as the Food and Drug Administration (FDA). This might explain why clinical trials were non strict.

CONCLUSION

In conclusion, on the basis of the scientific evidences presented by Nicolson *et al*., new nutritional supplements have been entering the market. Metagenics® (Northgate, Brisbane, Australia) has recently produced the Omega Brain Plus®, made of omega 3, vitamin D, phosphatidylcoline and phosphatidylserine. Together these lipid factors affect the inflammatory system and the peroxidised lipid membrane [1-5, 9, 15-24, 27, 28], decreasing cell aging rate and oxidative stress damage. LRT relies on natural products, free of side effects, which might be added as a nutritional supplement to the standard therapy in patients with fatigue. Moreover, empirical results of its administration have yielded good results, as reported on the internet [29] and medical periodical [30]. Therefore, despite the concerns and criticisms, the important results obtained through clinical trials and the innovative idea to replace damaged lipids with new effective lipids, necessary for ATP production, deserve more research.

REFERENCES

[1] Barenholz Y, Yechiel E. Lipid replacement therapy. U.S. Patent. 4812314. 1989 Mar 14.

[2] Yechiel E, Barenholz Y. Cultured heart cell reaggregates: a model for studying relationships between aging and lipid composition. Biochim Biophys Acta 1986; 859: 105-9. http://dx.doi.org/10.1016/0005-2736(86)90323-8

[3] Yechiel E, Barenholz Y. Relationships between membrane lipid composition and biological properties of rat myocytes. effects of aging and manipulation of lipid composition. J Biol Chem 1985; 260: 9123-31.

[4] Yechiel E, Henis YI, Barenholz Y. Aging of rat heart fibroblasts: Relationship between lipid composition, membrane organization and biological properties. Biochim Biophys Acta 1986; 859: 95-104. http://dx.doi.org/10.1016/0005-2736(86)90322-6

[5] 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: 22-8.

[6] Hamilton JA. Fatty acid transport: Difficult or easy? J Lipid Res 1998; 39: 467-81.

[7] Fellmann P, Herve P, Pomorski T, *et al*. Transmembrane movement of diether phospholipids in human erythrocytes and human fibroblasts. Biochemistry 2000; 39: 4994-5003. http://dx.doi.org/10.1021/bi992649q

[8] 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: 605-12.

[9] Seidman MD, Khan MJ, Tang WX, Quirk WS. Influence of lecithin on mitochondrial DNA and age-related hearing loss. Otolaryngol Head Neck Surg 2002; 127: 138-44. http://dx.doi.org/10.1067/mhn.2002.127627

[10] Appel S, Chapman J, Shoenfeld Y. Infection and vaccination in chronic fatigue syndrome: myth or reality? Autoimmunity 2007; 40: 48-53. http://dx.doi.org/10.1080/08916930701197273

[11] Manuel y Keenoy B, Moorkens G, Vertommen J, De Leeuw I. Antioxidant status and lipoprotein peroxidation in chronic fatigue syndrome. Life Sci 2001; 68: 2037-49. http://dx.doi.org/10.1016/S0024-3205(01)01001-3

[12] Richards RS, Roberts TK, McGregor NR, Dunstan RH, Butt HL. Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome. Redox Rep 2000; 5: 35-41. http://dx.doi.org/10.1179/rer.2000.5.1.35

[13] Pall ML. Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome. Med Hypotheses 2000; 54: 115-25. http://dx.doi.org/10.1054/mehy.1998.0825

[14] Radi R, Rodriguez M, Castro L, Telleri R. Inhibition of mitochondrial electron transport by peroxynitrite. Arch Biochem Biophys 1994; 308: 89-95. http://dx.doi.org/10.1006/abbi.1994.1013

[15] Agadjanyan M, Vasilevko V, Ghochikyan A, *et al*. Nutritional supplement (NT factor™) restores mitochondrial function and reduces moderately severe fatigue in aged subjects. J Chronic Fatigue Syndrome 2003; 11: 23-36. http://dx.doi.org/10.1300/J092v11n03_03

[16] Nicolson GL, Ellithorpe RR, Ayson-Mitchell C, Jacques B, Settineri R. Lipid replacement therapy with a glycophospholipid-antioxidant-vitamin formulation significantly reduces fatigue within one week. J Am Nutraceut Assoc 2010; 13: 10-14.

[17] Ellithorpe RR, Settineri R, Nicolson GL. Pilot study: reduction of fatigue by use of a dietary supplement containing glycophospholipids. J Am Nutraceut Assoc 2003; 6: 23-8.

[18] Colodny L, 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; 3: 17-25.

[19] Ellithorpe RR, Mitchell CA, Settineri R, Nicolson GL. Lipid replacement therapy drink containing a glycophospholipid formulation rapidly and significantly reduces fatigue while improving energy and mental clarity. Funct Food Health Dis 2011; 8: 245-54.

[20] Nicolson GL, Settineri R, Ellithorpe R. Lipid replacement therapy with a glycophospholipid formulation with NADH and CoQ10 significantly reduces fatigue in intractable chronic fatiguing illnesses and chronic lyme disease patients. Int J Clin Med 2012; 3: 163-70. http://dx.doi.org/10.4236/ijcm.2012.33034

[21] 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 Food Health Dis 2011; 4: 135-60.

[22] 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: 543-52. http://dx.doi.org/10.1007/s10555-010-9245-0

[23] Nicolson GL, Conklin KA. Reversing mitochondrial dysfunction, fatigue and the adverse effects of chemotherapy of metastatic disease by molecular replacement therapy. Clin Exp Metastasis 2008; 25: 161-9. http://dx.doi.org/10.1007/s10585-007-9129-z

[24] Nicolson GL. Lipid replacement/antioxidant therapy as an adjunct supplement to reduce the adverse effects of cancer therapy and restore mitochondrial function. Pathol Oncol Res 2005; 11: 139-44. http://dx.doi.org/10.1007/BF02893390

[25] Yancey JR, Thomas SM. Chronic fatigue syndrome: diagnosis and treatment. Am Fam Physician 2012; 86: 741-6.

[26] Piper BF. Piper fatigue scale available for clinical testing. Oncol Nurs Forum 1990; 17: 661-2.

[27] Berquin IM, Edwards IJ, Kridel SJ, Chen YQ. Polyunsaturated fatty acid metabolism in prostate cancer. Cancer Metastasis Rev 2011; 30: 295-309. http://dx.doi.org/10.1007/s10555-011-9299-7

[28] Querfeld U. Vitamin D and inflammation. Pediatr Nephrol 2013; 28: 605-10. http://dx.doi.org/10.1007/s00467-012-2377-4

[29] Jostin L. Cargo Cult Science and NT Factor®. 2010. http://www.genetic-inference.co.uk/blog/2010/01/cargo-cult-science-and-nt-factor/

[30] Segna R, Rosenblatt S, Jimenez A. Lipid replacement therapy for cancer fatigue, hormone dysfunction, and gut inflammation. Focus Allergy Research Group 2012: 11-12. http://content.yudu.com/Library/A1y5jw/FocusAllergyResearch/resources/index.htm?referrerUrl=https%3A%2F%2Fwww.google.it%2F

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