Lipids preserve the fluidity and functionality of biomembranes. Integrative clinicians reasonably use this as the scientific basis of oil therapies in the treatment of fibromyalgia (FM) and chronic fatigue syndrome (CFS). However, there is much more to lipid biology. Lipids are information molecules that serve crucial roles in cellular signaling systems. Lipid signals integrate energetic, metabolic, detoxification, inflammatory, regenerative, and death pathways. Specifically, the importance of lipid signals in the pathogenesis of a cluster of chronic metabolic disorders – fatty liver change, insulin resistance, hyperinsulimia, prediabetes, syndrome X, the so-called metabolic syndrome, type 2 diabetes, atherosclerosis, and others – is well-documented. The consequences of disruption of lipid signals in the pathogenesis of FM, CFS, and related energy deficit disorders are seldom, if ever, duly considered.

In my last column, I described the application and clinical benefits of Castor-Cise in the treatment of FM, CFS, and related energy deficit disorders. Castor-Cise is an integrated program of liver and bowel detox with topical castor oil application, oral detox with vigorous sesame oil rinses, and limbic (meditative) exercise. Patients commonly report strong benefits of Castor-Cise and often ask how castor oil works. My colleagues wonder how the castor oil applied to the skin overlying the liver crosses the barrier imposed by the pleural sac to reach the liver. Later in this communication, I offer a hypothesis concerning the mechanisms of action of castor oil and, by extension, of other oils such as sesame, mustard, and calendula oils.

A Battery for a Flashlight
An image of an empty flashlight and battery appears as I write about lipid signals. A protein that binds lipids can be visualized as the lifeless shell of a flashlight. A lipid, in this analogy, is then seen as a battery. Just as a battery brings energy, life, and light to a flashlight, a lipid molecule brings life to a lipid-binding protein molecule and initiates its lipid-related activities. Lipids have to occupy the “lipid pockets” of the lipid-binding proteins – the domains of the protein molecules that provide the space in which the lipids fit snugly – before the action can begin. What would be expected if the lipid-binding protein molecule is bent or twisted and the lipid pocket is unable to accommodate the lipid? The answer: the lipid signal would be absent or distorted. Advances in proton magnetic resonance spectroscopic imaging (H-MRSI) make it possible to examine the topography of lipid-binding proteins and functional aspects of lipid signals. Notably, it is now possible to distinguish between lipid signals and signals from other elements, such as of H+ derived from lactic acid. I present the results of some applications of H-MRSI technology to illustrate this point.

In this column, I explore aspects of the physiology and pathology of lipid signaling and show the relevance of cross contamination and other forms of disrupted lipid signals to both the pathogenesis and control of FM and CFS. To put such information in a broader context of basic sciences and clinical medicine, I address the following subjects: (1) a brief review of recent advances in delineation of lipid signals with proton magnetic resonance spectroscopic imaging (H-MRSI); (2) the good-HDL-bad-LDL cholesterol folly; (3) importance of understanding dysfunctional lipid signaling within the larger context of disrupted oxygen signaling (dysoxygenosis); (4) a hypothesis concerning the mechanisms of action of topical castor and other oil therapies; (5) my clinical priorities for reversing FM and CFS with non-drug oxystatic therapies; and (6) long-term clinical outcome data obtained with such therapies.
Lipids are classified as (1) neutral fats, (2) phospholipids, (3) cholesterol, and (4) a miscellaneous group including waxes. Triglycerides are examples of neutral fats that are broken down by the enzyme triglyceride lipase (epinephrine and norepinephrine are the two major hormones that activate the enzyme) to release glycerol and free fatty acids. The average blood concentrations of triglycerides and phospholipids are the same: 160 mg/dL. Apolipoproteins in various lipoprotein particles maintain cholesterol homeostasis, as well as direct ligand-receptor dynamics at biomembranes and within cellular organelles.

**Lipid Signals and Defenses Against Microbes**

In man-microbe conflicts (described in my column of May 2005), lipid signals are important weapons used by both sides. Specifically, chemotaxis, the process by which cells attract other cells, involves lipid signals. Chemotactic cells accumulate a class of lipids called phosphoinositides at the leading edge of the cell. These lipids are then bound to lipid-binding domains of various signaling proteins. As a result, the lipid batteries "energize" the protein shells of the so-called signaling proteins. For example, during phagocytic chemotaxis in Dictyostelium, the specificities of various domains of lipid-binding proteins for particular phosphoinositides enables them to distinguish between — and compare and sort out — lipid signals under different conditions. It is noteworthy that the properties of the protein domains are also critical to the recognition of localized signals in polarized cells.

**Lipid Signals, Metabolism, and Immunity**

Lipids signals form crucial components in the intelligence network of the body. How do lipids couple to target signaling and metabolic pathways? How is their intracellular trafficking regulated? These questions are being vigorously investigated. One such line of inquiry concerns the family of cytoplasmic fatty-acid-binding proteins (FABPs). These are 14B15-kDa proteins that have a high affinity for hydrophobic ligands, including saturated fatty acids, unsaturated long-chain fatty acids, eicosanoids (such as hydroxyeicosatetraenoic acid), leukotrienes, and prostaglandins. The adipocytes (fat cells) express one member of the FABP family called FABP4 (also referred to as aP2) under the influence of peroxisome-proliferator-activate receptor-PPAR agonists, insulin and fatty acids. Another crucial system of cytoplasmic fatty-acid-binding proteins involves FABPs produced by macrophages, the scavenger cells of the body. The deficiency of macrophage-specific aP2-deficiency leads to a marked protection against early and advanced atherosclerosis in apolipoprotein E-deficient (Apoel-/-) mice. The lipid-binding protein aP2 affects many aspects of the so-called metabolic syndrome. (See my column entitled "The Dysox Model of Diabetes and De-Diabetization Potential" in the May 2007 issue of Townsend Letter for a deconstruction of the term metabolic syndrome.) Studies in mice have shown that deficiency of aP2 partially protects mice against insulin resistance associated with genetic or diet-induced obesity. The fat cells (adipocytes) of mice without the aP2 gene have reduced efficiency of lipid transport both under in vitro (in the laboratory) and in vivo (in living animals) conditions. The aP2 protein is also expressed in macrophages (scavenger cells). In such cells, it is regulated by several types of lipids, including myristic acid, lipopolysaccharide, oxidized low-density lipoproteins, and PPAR ligands. The strength and quality of lipid signals in human muscles have been examined with proton magnetic resonance spectroscopic imaging (H-MRSI). Significant differences in lipid signals in the muscle tissues of nonobese sedentary, obese sedentary, moderately trained athletes, and diabetic individuals. Specifically, abnormal lipid signals-designated cross contamination have been found in muscle cells. Such abnormalities correlate with muscle type, training status, and the presence of obesity and type 2 diabetes.

**Separation of Lipid and Lactate Signals**

Proton magnetic resonance spectroscopy (MRS) has also been used to isolate lactate signals from lipid signals in the ischemic brain. In such studies, MRS is first used to delineate the lipid and lactate components of a spherical phantom in vitro, and the parameters are established to separate these components in vitro. Infarction of brain tissues is produced in rats using the middle cerebral artery occlusion, and magnetic resonance measurements are obtained from the brain tissues. Such studies have shown that lipids have shorter relaxation times and lactates have longer ones. Consequently, these distinct magnetic characteristics permit separation of the lactate signal from the lipid signal.

**Abnormal Cholesterol Signaling in FM and CFS**

Cholesterol signaling plays central roles in diverse intelligence, metabolic, and hormonal functions in health and disease. Fibromyalgia and CFS, as I explain later, are caused by impaired oxygen homeostasis, a state characterized by respiratory-to-fermentative shift in mitochondrial ATP production, abnormal cell membrane function, and deranged matrix signaling. Not unexpectedly, cholesterol homeostasis is disturbed in FM and CFS. In general, the longer and more severe the clinical disease, the lower the blood cholesterol levels. I have seen levels as low as 85 mg/dL. I recognize this as a clear indication of liver dysfunction. During the early months of illness, the blood cholesterol levels rise in some individual as a consequence of incremental acidotic, oxidative, coagulative, and dysoxic stresses.

Statin drugs administered to lower cholesterol levels commonly cause fatigue and muscle problems in individuals without myalgia and undue fatigue. Not unexpectedly, statins compound the myalgic and fatigue symptoms in
patients with FM and CFS. It is also noteworthy that the liver detox pathways are also commonly impaired in these disorders. The existence of liver injury can be readily established in nearly all such patients by documenting increased urinary excretion of hippuric acid and other indicators of impaired hepatic detox pathways. The liver plays crucial roles in maintaining lipid-protein interactions – how protein packaging alters lipid signals, for instance – in the body. For those considerations, I consider the use of statin drugs in such patients inadvisable. To underscore the enormous complexity of lipid/protein dynamics in health and disease and to focus on abnormal cholesterol signaling, below I discuss some aspects of cholesterol homeostasis, with focus on the widely misunderstood LDL/HDL cholesterol story.

The Good-Cholesterol-Bad-Cholesterol Folly
I am amused when I hear LDL cholesterol is “bad” and HDL cholesterol is “good.” As far as I know, cholesterol has one molecular formula and one molecular structure. How does one cholesterol molecule become both “good” and “bad” at the same time? The answer: cholesterol is cholesterol is cholesterol; the notions of goodness of one cholesterol and badness of another cholesterol are artifacts of thinking. I have never heard any cholesterol expert address this matter. Why? Could it be because statin makers make so much money with the good-HDL-bad-LDL story that they can buy any and all cholesterol experts. I consider it to be the single most important consideration in the entire field of “cholesterolology,” since it exposes well the buffoonery of the HDL/LDL merchants better than any other. In 1997, I addressed this crucial subject in a long review article. Below, I reproduce some text from that article which is of special relevance to the present context:

Lipid-Protein Redox Ecosystems
Lipids in plasma membranes are essential for membrane fluidity, surface potentials, surface ligand activity, and transport functions. To serve these diverse functions, lipids exist in blood and plasma membranes not as discrete molecular species – as it might seem from the conventional description of lipid chemistry – but as dynamic “lipid redox ecosystems” in which external pro-oxidant influences are vigorously counterbalanced by antioxidant defenses that exist within the lipid particles. For example, low-density lipoprotein (LDL) particles occur as spherical particles, with diameters ranging from 19-25 nm, molecular weight varying over a broad range from 1.8 to 2.8 million, and the density ranging from 1.019 to 1.063 g/ml. LDL is a large lipoprotein complex that includes the following: cholesterol moieties (estimated 1600 and 600 molecules of cholesterol esters and free cholesterol, respectively), triglycerides (estimated 170 molecules), phospholipids (estimated 700 molecules), and...
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apolipoprotein B, neutral and polar lipids, including polyunsaturated fatty acids, and lipophilic antioxidant species such as beta carotene and vitamin E. Predictably, the antioxidant content of LDL varies over a broad range and appears to be diet-related. Lipoprotein (a) [Lp (a)] is structurally similar to LDL but is distinguished from it by the presence in it of a highly glycosylated protein designated apoliprotein(a). It binds to apolipoprotein B (apo B)-containing lipoproteins and proteoglycans. It has a complex relationship between fibrin, platelets, and atherogenesis. By its high affinity for and binding with fibrin, it activates plasminogen, while its binding to platelet receptors leads to plasminogen binding and activation. Lp(a) is considered atherogenic because it is taken up by foam cells; however, elevated levels are associated with IHD [ischemic heart disease] in most, but not all, reports. We now return to the subject of spontaneity of oxidation in nature to put the notion of lipid redox ecosystems into perspective.

At a fundamental level, cholesterol homeostasis in the cells is maintained by the way cholesterol is presented to the cell membrane by lipid-protein particles. The receptor-ligand dynamics of lipoproteins are profoundly influenced by the structural and functional characteristics of "protein packaging" of lipids. When cholesterol molecules have one type of protein packaging (including apolipoprotein A), the cluster of cholesterol molecules becomes "protein-dense" and so become high-density lipoprotein cholesterol (HDL, subdivided into HDL-1 and HDL-2). In such protein packaging (integrated with cholesterol esters, triglycerides, phospholipids, and other lipids), cholesterol is claimed to protect arteries against oxidative injury and deranged oxygen signaling. By contrast, when cholesterol molecules have another type of protein packaging (including apolipoprotein B), the cluster of cholesterol molecules becomes "protein-light" and so becomes low-density lipoprotein cholesterol (LDL). It is claimed that cholesterol in this configuration is not able to protect arteries against oxidative injury and deranged oxygen signaling. The very low-density lipoprotein cholesterol is the variety with even less protein.

Several layers of complexity are added by heterogeneity of five classes of apolipoproteins (A,B,C,D, and E). As indicated above, apolipoprotein A-I (ApoA-I) is the major protein component of high-density lipoprotein (HDL) in plasma. It promotes cholesterol efflux from tissues to the liver for excretion. Apolipoprotein B (APOB) is the primary apolipoprotein of LDL lipoproteins, and primarily transports cholesterol to tissues. It is noteworthy that there are more than 100 known variations of apolipoproteins created by genetic polymorphisms. Another layer of complexity is added by lipoprotein a {Lp(a)}, a lipoprotein that resembles LDL in composition with an abnormal protein, termed [a], attached to it. Lp(a) is structurally similar to plasminogen, an important protein in the fibrinolytic (clot-busting) enzyme systems of the body. By competitive inhibition of plasminogen, Lp(a) inhibits clot-busting and increases the risk of coronary heart disease. Approximately one-third of individuals with coronary heart disease have elevated Lp(a) levels.

Physical exercise raises HDL cholesterol levels. What might be the mechanism(s) underlying this phenomenon? The blood LDL cholesterol levels rise with incremental oxidative stress (unpublished personal observation). What biochemical phenomena might underlie this relationship? Statins interrupt normal sleep patterns. Statins increase the risk of cancer. Statins, as indicated earlier, cause liver and muscle injury. What might be the energetic-molecular basis of those relationships? I propose that these variations occur due to changes in the production of apolipoprotein A and B production in the liver, which, in turn, are induced by changing redox conditions and oxygen signaling in the various organ-systems of the body. In a previous column ("The Dysox Model of Diabetes and De-Diabetization Potential"), I drew the analogy of a crank and a crank-shaft to explain hyperinsulinism and insulin resistance. A crank easily transmits rotary motion to a well-oiled crank shaft. A crank cannot do so if the crank-shaft is rusty or twisted. When the crank of insulin is unable to efficiently

Figure 1. The Three-Legged Throne of Oxygen Stabilized by the Three Primary Regulatory Mechanisms Governed by Oxygen. Cue Stands for Clotting-Unclotting Equilibrium

Figure 2. Three Macro-Furies That De-stabilize the Oxygen Throne

Figure 3. Three Micro-Furies That Destabilize the Oxygen Furies

Figure 4. The Oxygen Throne and the Three M Model of Disease
turn the crank-shaft of an insulin receptor embedded in a chemicalized and hardened cell membrane, the pancreas responds by producing more insulin to overcome the resistance of the impacted insulin receptor. This is the basis of hyperinsulinism and insulin resistance. The same holds for the LDL cholesterol and LDL lipoprotein receptor.

The oxygen conditions of the cell membrane determine the lipid/ligand dynamics. This is as true of lipid-lipid receptor dynamics as it is of insulin-insulin receptor dynamics. Seen in this light, the cholesterol problem is, in reality, a problem of protein packaging. Since I recognize protein disorders to be caused by toxic environment, toxic foods, and toxic thoughts, I considered the so-called cholesterol problems to be caused by the trio of toxicities of environment, foods, and thoughts. It is highly significant in this context that most of the lipoproteins are produced in the liver, an organ that bears the brunt of endogenous and exogenous toxins. Also, I consider this to be the scientific basis of detox procedures for normalizing cholesterol homeostasis. In light of these considerations, it is not surprising that statin drugs that lower blood cholesterol levels do not reduce the incidence of coronary artery disease in women (see "Why Statins Do not Work for Women" at www.majidali.com).

Understanding Abnormal Lipid Signals in the Context of the Dysox State

In Leaky Cell Membrane Dysfunction (1987), I discussed the clinical evidence for increased cell membranes permeability dysfunctions in patients with oxidosis. In a subsequent publication, I described morphologic evidence of cell membrane injury. Those observations led me to hypothesize that oxidosis causes leakage out of cells of elements that occurs predominantly within them - potassium, magnesium, taurine, glutathione, and others - and influx into cells of predominantly extracellular elements, such as calcium. This would explain the observed benefits of liberal potassium and magnesium supplementation in integrative medicine, as well as of calcium channel blocker drugs in pharmacologic regimens.

In 1998, I described biochemical and morphologic evidence to link the pathogenesis of FM and CFS to dysoxygenosis, a state characterized by uncoupling of oxidative phosphorylation from respiration and respiratory-to-fermentative shift. Those and other studies led to the publication of Oxygen and Aging (2000), a volume devoted to oxygen homeostasis in health and disease. In subsequent publications, I further examined the central roles of oxygen signaling in chronic inflammatory, autoimmune, degenerative, and neoplastic disorders.

In Darwin's Drones, Dysox, and Diabetes (2008), I summarized the results of earlier studies to show how oxygen governs human biology by controlling three primary homeostatic mechanisms: acid-alkali balance, redox regulation, and clotting-unclotting equilibrium. The three regulatory mechanisms, in turn, support the master homeostatic functions of oxygen. To illustrate these relationships, in Darwin, Dysox, and Diabetes, I put forth an analogy of the "oxygen king" and its three "executive branches" for maintaining law and order in the body. Those three executive (regulatory) branches are acid-alkali balance (AAB), oxidant-antioxidant regulation (OAR), and clotting-unclotting equilibrium (CUE). To illustrate that analogy, I put forth a schema of the "Three-Legged Throne of Oxygen," a simple diagram to show how the throne is supported and stabilized by its three executive branches - the three integrated regulatory systems of AAB, OAR, and CUE (Figure 1).

The first core point of the analogy of the three-legged throne is that any weakness in any leg de-stabilizes the throne. So, disturbances in AAB cause disorder in the other two (OAR and CUE).

The "oxygen throne" is destabilized by toxicities of environment, foods, and thoughts (Figure 2). Any threat to one of the legs of this throne stresses and eventually weakens the other two legs.

Excess acidity causes excess free radical activity and increases clotting ability ("clottability") of bodily fluids. Excess oxyradical (oxygen-derived free radical) activity causes excess acidity and increases clottability of bodily fluids. Any and all factors that increase clottability of bodily fluids cause excess acidity and excess oxyradical activity (Figure 3). The biochemical consequences of acidosis, oxidosis, and CUE are borne by cell membranes, matrix, and mitochondria - the 3-M regulatory systems of the body (Figure 4).

How Does Castor-Cise Work?

Based on the biochemical, clinical, and therapeutic consideration discussed in this column, I propose that topical castor oil applications exert their clinical benefits.

> Figure 5. Clinical Response to Integrative Oxystatic Therapies in 150 Patients with fibromyalgia. Excellent 65.4%, Good 19.3, Fair 5.3, and Poor 10%.
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by restoring oxygen homeostasis. Following are the mechanisms that, singly or in concert, facilitate delivery of oxygen into the cells and improve efficiency of oxygen-driven energetic, detox, and repair pathways:

• restoration of cell membrane fluidity;
• increased delivery of oxygen through restored cell membrane fluidity;
• improved lipid and protein signaling;
• enhanced lipid-ligand dynamics at biomembranes;
• normalization of membrane ion channel functions;
• restoration of normal electromagnetic gradients;
• direct detergent effect of vigorous oral sesame oil rinses for removal of fat-soluble toxins produced by oral microbial population;
• correction of acidosis, oxidosis, and clotting-unclotting equilibrium; and
• potent anti-inflammatory effects accruing from all of the above elements.

All of the above mechanisms facilitate entry of oxygen by direct diffusion across the cell membrane and possibly by their normalized paramagnetic effects.

Clinical Priorities for Reversing FM and CFS

Following are my top priorities among low-cost and highly effective therapies for reversing FM and CFS:

• Self-regulation with meditation and limbic breathing (see July 2007 column)
• Elimination of sugar, dairy, and wheat for six to 12 weeks
• Bowel and liver detox with Castor-Cise (see December 2007 column)
• Dr. Ali’s breakfast with flaxseed, lecithin, protein powder, and organic vegetable juice (see May 2007 column)
• Peroxide foot soaks (see October 2004 column)
• Mineral supplement (magnesium, 1,000 to 1,500 mg; potassium, 150 to 300 mg; zinc, 25 to 50 mg)
• Redox-restorative sulfur nutrients (see glutathione, MSM, taurine, alpha lipoic acid)
• Anti-inflammatory spices and antioxidants, especially 1 gm vitamin C + one-half teaspoon of turmeric powder three times a day, ginger, garlic, and onions
• Antifungal therapies (see October 2006 column)

In my October 2006 column, “Hurt Human Habitat and Energy Deficit States,” I furnished detailed descriptions of my sun-soil model of clinical priorities for restoring cellular energy systems. Briefly, in this model: (1) the roots of a plant symbolize the bowel, blood, and liver ecosystems; (2) branches of the plant represent the trio of the thyroid, adrenals, and pancreas; and (3) leaves and flowers connote the trio of neurotransmitters, hormones, and the limbic brain. I provided specific information about my preferences for detoxifying and/or supporting all these ecosystems.

Results of a Clinical Outcome Study of Patients with Fibromyalgia

In 1998, my colleagues at the Institute of Integrative Medicine, New York, and I published the results obtained in a series of 150 patients with FM/CFS complex treated with integrative oxystatic therapies. The main components of this program were the following: (1) patient education of all major nutritional, ecologic, and dysox issues concerning the cause and reversal of the FM/CFS complex; (2) optimal food choices; (3) oral redox-restorative and oxystatic nutritional and herbal protocols designed to arrest and reverse the dysox state; (4) intramuscular and intravenous protocols to potentiate the various enzymatic pathways of the body, especially those involved in oxygen transport and utilization, acid-base equilibrium, and hepatic detoxification; (5) direct oxystatic therapies, including nasal oxygen, intravenous infusions of hydrogen peroxide, ozone, and chelating agents; (6) specific protocols for restoring microecologic cellular and macroecologic tissue-organ ecosystems, especially the bowel, blood, and liver ecosystems (including such empirically effective therapies as colon hydrotherapy); (7) support for the thyroid, adrenals, and pancreas trio; (8) support for sex hormones, neurotransmitters, and hypothalamic-limbic system; and (9) stress management with self-regulation, meditation, and limbic stretching. In Tables 1 and 2, I present the demographics of my patients and improvement in outcome scores. The overall final outcome scores for all 150 patients were as follows: excellent outcome, 65.4%; good, 19.3%; fair, 5.3%; and poor, 10% (Figure 5).
In closing, fibromyalgia and chronic fatigue syndrome are energy-deficit disorders characterized by uncoupling of respiration from oxidative phosphorylation and abnormal oxygen signaling. Abnormalities of lipid signaling caused by environmental, nutritional, and stress-related elements are important contributory factors in the etiology of abnormal oxygen signaling which, in turn, compounds the problems of lipid signaling. I have documented strong clinical benefits of topical castor oil applications for liver and bowel detoxification integrated with limbic, meditative exercise (Castor-Cise) for relieving symptoms of FM and CFS. A hypothesis explaining the scientific basis and/or rationale for the use of Castor-Cise is presented.

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