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## REPORT

Fats for Life

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Imagine a kind of fat that could help reduce cholesterol levels, lower blood pressure, fight dementia and slow down the aging process. This fat would be better than any known drug. Best of all, it is not a fantasy but a reality. We are talking about certain polyunsaturated, natural fatty acids, whose beneficial effects have been documented in thousands of studies over the last decade. Of crucial importance, however, is taking the right essential fatty acids in the correct balance.

Years of conflicting messages about the role of fat in our diet have caused much confusion and even skepticism toward new information. In spite of scientific progress, few commercial messages today are based on current scientific knowledge. Instead they are deliberate half-truths and misinformation from companies eager to sell their “fat-free” and “cholesterol-free” products. Hidden are the facts that the sugar and hydrogenated fats in their products are the real culprits that will increase the body’s own production of cholesterol or other unhealthy fats, causing exactly the damage thought to be avoided.

Fat is necessary for life. It is a key component in body chemistry and energy storage. Knowing the difference between the beneficial essential fatty acids (EFAs) and the harmful fats is of crucial importance for health and longevity. Extensive research has made it clear that a reduced or imbalanced intake of EFAs plays a significant role in the development of many cardiovascular, neurological, metabolic and other age-related degenerative diseases.

This research has singled out two particularly beneficial fatty acids, GLA and DHA, and pointed to an ideal balance between them that could guard against disease and age-related disorders in many-fold ways. These key fatty acids protect the cardiovascular system, lowering blood pressure, raising good (HDL) cholesterol while lowering bad (LDL) cholesterol and triglyceride levels. They reduce stress reactions, and may ameliorate insulin resistance. GLA helps reverse the effects of aging on fatty acid metabolism, while DHA is essential to the development and maintenance of brain functions, being of crucial importance for children, as well as for the elderly in prevention and treatment of dementia.

The richest known source of GLA is borage oil (23% GLA), while DHA is plentiful in cold water fish. GLA and DHA make a wonderful team for health and longevity.

Omega-3 and omega-6 oil

Fatty acids serve as building blocks of nerve cells, cell membranes and biochemical messengers such as prostaglandins. Essential fatty acids (EFAs) cannot be produced within the body and therefore must be provided through the diet. If the diet is lacking in EFAs, saturated fats will take the place of EFAs within cell membranes, reducing membrane fluidity and efficiency, and thereby starting a process of premature aging and disease development. In addition, by taking the right kinds of EFAs in the right proportions, we can maximize the production of beneficial prostaglandins and other chemical messengers, while minimizing production of harmful ones.

There are two families of EFAs: omega-3 and omega-6 fatty acids. Experimental studies confirm that a balanced combination of these two families is essential for maximal effect in lowering blood pressure, improving the serum lipid profile and reducing atherosclerosis. When dietary omega-6 and omega-3 oils were used separately and in combination in a study on the regression of experimental atherosclerosis in rabbits, cholesterol levels decreased faster in the group fed the combination oils. In this group there was also a three-fold reduction of atherosclerotic plaques in the aorta compared to untreated animals (Khalilov et al., 1997).

An ambitious study of different ratios and dosages of EFAs, given to 20 Vervet monkeys over a 12 weeks period, documented the importance of getting these essential fatty acids in the right proportion. The results indicate that a combination of omega-6 and omega-3 (in this case, GLA and EPA), in a proportion ranging from 2:1 to 4:1 (two to four parts of omega-6 to one part of omega-3), is the ideal combination to reduce bad LDL cholesterol, raise good HDL cholesterol and thus improve the LDL/HDL cholesterol ratio (van Jaarsveld et al., 1997).

This finding conforms with recommendations by a number of health agencies around the world, including the World Health Organization, the British Nutrition Foundation and the Japan Society for Lipid Nutrition. Based on evidence that an elevated ratio of omega-6 to omega-3 fatty acids is a major risk factor for many chronic diseases, these agencies recommend a ratio ranging from approximately 2:1 to 4:1 (Horrocks et al., 1999). Due to the disproportionate level of omega-6 oils in the typical American diet, it is preferable to supplement at the lower end of this range, at a ratio of two parts omega-6 to one part omega-3 oils.

### GLA & DHA

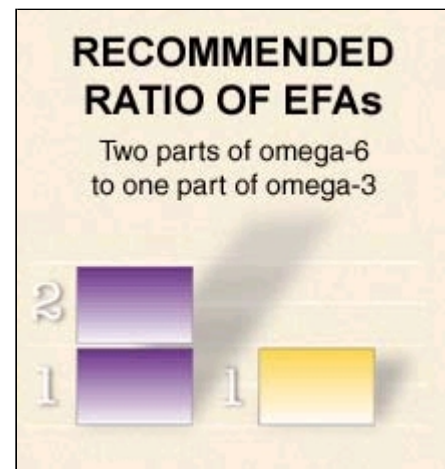
To express their full biological activity, the two "parent" EFAs, linoleic acid (omega-6) and alpha-linolenic acid (omega-3) must be metabolized in several steps with the help of important enzymes. In this process GLA (gamma-linolenic acid) is produced from linoleic acid, and DHA (docosahexaenoic acid) as well as EPA (eicosapentaenoic acid) from alpha-linolenic acid. The high ratio of linoleic acid (omega-6) to alpha-linolenic acid (omega-3), typically found in western diets, will inhibit both the uptake and the conversion of alpha-linolenic acid due to competition for the same enzymes between the two EFAs.

The first step in both these conversion processes is controlled by the enzyme D6D (delta-6 desaturase). Unfortunately, D6D activity declines with age, and is reduced in some individuals even at a younger age (Horrobin, 1981). This not only inhibits the synthesis of GLA and DHA, but also leads to a prostaglandin imbalance with decline of the good series-1 and series-3 prostaglandins and other beneficial eicosanoids, which exhibit potent anti-inflammatory and immunoregulatory effects. The reduced capacity to convert parent EFAs to GLA and DHA is associated with conditions including cardiovascular disease, diabetes, alcoholism, atopic dermatitis, premenstrual syndrome, rheumatoid arthritis and cancer (Bolton-Smith et al., 1997; Leventhal et al., 1993; Horrobin, 1993), as well as learning deficits and development of dementia.

The exciting news is that supplementation with GLA and DHA can circumvent impaired D6D function, and restore levels of the good prostaglandins. Moreover, GLA supplementation actually increases D6D activity, reversing the effect of aging on the enzyme itself (Biagi et al., 1991). In this way, GLA supplementation improves the metabolism of both omega-6 and omega-3 fatty acids. It has also become clear that the omega-3 fatty acids DHA and EPA limit the production of the bad series-2 prostaglandins by preventing the release of arachidonic acid from cell membranes, inhibiting its further metabolism. A high amount of linoleic acid (omega-6), on the other hand, limits the availability of alpha-linolenic acid (omega-3) as a precursor for the good series-3 prostaglandins and stimulates the formation of arachidonic acid, the precursor to the bad prostaglandins (series-2) and other pro-inflammatory eicosanoids.

Biagi et al. (1991) studied both old and young rats that were fed either a GLA-rich diet or a control diet. Old animals fed the control diet showed a clear decline in the level of delta-6-desaturated metabolites of both the omega-6 and the omega-3 series. In the GLA group of old mice there was no decline of these metabolites.

A study of more than 10,000 middle-aged men and women in Scotland showed that aging influences the fatty acid composition of adipose (fatty) tissue independently of diet (Bolton-Smith et al., 1997). The study confirms the earlier mentioned experimental



Getting the omega-6 and omega-3 fatty acids in the right proportions can reduce bad LDL cholesterol and raise good HDL cholesterol

**Prostaglandins  
The Good and Bad**

Too much prostaglandin E2 can lead to degenerative disease, whereas high levels of beneficial prostaglandin E1 and E3 protect the body. Here is a brief description of how these prostaglandins function in the body:

- Prostaglandin E1 prevents blood platelets from sticking together, thereby helping to prevent heart attacks and strokes caused by blood clots. It relaxes blood vessels, improving circulation and lowering blood pressure. It reduces inflammation, makes insulin work more effectively and enhances the T-cell function of the immune system. GLA increases this beneficial prostaglandin.
- Prostaglandin E2 promotes platelet aggregation, the first step to clot formation, increasing the risk for heart attack and stroke. It makes the kidneys retain sodium, leading to water retention, and it causes inflammation. Diets high in saturated fats (arachidonic acid) increase levels of this pro-inflammatory prostaglandin.

findings of an age-related decline in the rate-limiting step of delta-6-desaturation, and in addition discovered a greater decline in women than in men. The results indicate that an increase in dietary GLA could offset the age-related imbalance in fatty acid levels.

GLA and DHA both have preventive effects on atherosclerosis and heart attacks by lowering blood pressure and serum lipids and reducing cardiovascular reactions to stress. While GLA in addition has anti-aging effects, DHA has a unique role in the development and maintenance of the nervous system. It has proven to be important for development, learning and behavior in children as well as for prevention and treatment of dementia.

• Prostaglandin E3 has similar functions as prostaglandin E1. It also has a powerful effect of preventing the release of arachidonic acid stored in cell membranes and its conversion to prostaglandin E2. Omega-3 fatty acids are the source of this beneficial prostaglandin.

## Cardiovascular disease

Beneficial effects of both GLA and DHA on the cardiovascular system have been extensively documented in experimental and human studies: moderate but consistent blood pressure lowering effects, significant reductions of serum lipids, and beneficial influence on insulin resistance which plays a large role in the development of diabetes, atherosclerosis and heart attacks. Much research is currently focused on unraveling the many-fold mechanisms of action behind these favorable influences.

## Hypertension

Early detection is of great importance, since life style changes as well as medication is likely to prevent further development of serious complications. Incorporation of GLA and DHA in the diet has proven to be one of these changes that can reduce the blood pressure and help lower the risk of heart attacks, stroke and kidney failure.



In contrast to earlier beliefs, we now know that a stable systolic blood pressure (below 140 mmHg) is equally or even more important than a "normal" diastolic pressure (less than 90 mmHg). Systolic blood pressure increases with aging as a result of increased stiffness of the arteries and is a stronger predictor of risk in the elderly than the diastolic pressure. A pulse pressure (the difference between systolic and diastolic pressure) of more than 60 is a marker for advanced atherosclerosis and indicates a high risk for a cardiovascular event.

In most cases of hypertension (95%) no specific reason can be found for the elevated pressure, a condition known as essential or idiopathic hypertension. Results from a clinical, double blind, crossover study by Venter et al. (1988) support the hypothesis that deficiency of the enzyme D6D, so common in aging, may play an important part in the etiology of idiopathic hypertension. The study furthermore validates the earlier findings that a ratio of 2:1 of GLA and DHA/EPA is beneficial in prevention of cardiovascular diseases.

This trial involved 25 non-obese patients with mild-moderate essential hypertension. One group was given capsules containing 360 mg GLA and 180 mg EPA/day, while the other group received capsules containing only linoleic acid and alpha-linolenic acid, the parent EFAs that need the enzyme D6D for their metabolism to GLA and EPA/DHA. The average systolic blood pressure in the first group was significantly

reduced (~ 10 %) after 8 to 12 weeks of therapy, while there was no significant change in the second group, indicating that deficiency of the enzyme D6D is likely to promote an increase of blood pressure.

## Borage oil and DHA have blood pressure lowering effects

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Recently it has been discovered that elevated levels of the mineralocorticoid hormone aldosterone plays a much larger role in hypertension and cardiac disease than previously believed. Aldosterone-reducing drugs are used in the treatment of hypertension and have recently been discovered to be effective also for treatment of heart failure (Weber, 1999).

In addition to many other mechanisms of action, both GLA and DHA have now been found to inhibit aldosterone production, which may be a discovery of great importance in the prevention of cardiovascular disease.

One of the key mechanisms in the regulation of blood pressure is the renin-angiotensin-aldosterone system. Renin is released from the kidneys in response to low blood pressure and stimulates the production of aldosterone via several intermediate steps, including angiotensin I and II. Aldosterone controls sodium and water uptake in the kidneys, and elevated levels increase the blood pressure.

Not all cases of hypertension, however, are triggered through the renin-angiotensin system. So-called primary aldosteronism has traditionally been regarded as a rare cause of hypertension (1%) but has recently been discovered to be more frequent than earlier believed (10% to 15% of patients with essential hypertension) (Fardella et al., 1999). This condition is characterized by excess production of aldosterone in the adrenal gland, without involvement of the renin-angiotensin-aldosterone system. Characteristic features of primary aldosteronism are high aldosterone levels, low renin levels and a high aldosterone/renin ratio.

Since elevated aldosterone levels have been found to play such a major role in hypertension, a research team under Marguerite Engler investigated the relationship between GLA, DHA and aldosterone in animals. In several previous experimental studies Engler et al. had demonstrated that borage oil and DHA have blood pressure lowering effects in hypertensive, normotensive, old and young rats (Engler et al., 1992, 1993). When the scientists studied the effects of GLA and DHA on the renin-angiotensin-aldosterone system in rats, genetically programmed for hypertension (Engler et al., 1998 and 1999), it became clear that both these EFAs affect the renin-angiotensin-aldosterone system. Although in slightly different ways, both GLA and DHA decreased the production of aldosterone. In the GLA study the aldosterone/renin ratio was significantly lower in the borage oil group than in the control group given sesame oil. In the DHA study aldosterone was significantly lowered (33%) compared to the control group fed a diet containing corn/soybean oil. A remarkable reduction of the systolic blood pressure was also seen in both studies. In the borage oil group the decrease was 12 mmHg after three weeks, and in the DHA study the blood pressure was 34 mmHg lower on an average after six weeks.

The observations in these studies suggested that borage oil (GLA) inhibits the adrenal responsiveness to angiotensin II through diminished angiotensin receptor activity in aldosterone producing cells. Decreased aldosterone levels stimulate renin secretion and the net effect is a desirable reduction in the aldosterone/renin ratio. DHA on the other hand, appears to affect the aldosterone production without involving angiotensin receptors.

Kimura et al. (1995) found that DHA supplementation could to a large extent prevent an increase in blood pressure in rats genetically programmed to develop hypertension and stroke (spontaneously hypertensive rats). While the average blood pressure in the control group of young rats on "normal" diet increased from 120.2 to 202.9 mmHg during the test period, blood pressure in the DHA supplemented group only increased to 149.8 mmHg. Serum creatinine levels and blood urea nitrogen were significantly

## Basic Fat Chemistry

Fatty acids are distinguished by length (number of carbon atoms) and location of double bonds. Fatty acids with no double bonds are called saturated, while unsaturated fatty acids come with one or more double bonds. The double bonds change the biological function of the fatty acid.

Each molecule of fat, whether solid fat or liquid oil, is made up of three fatty acids attached to a glycerol molecule. Saturated fatty acids make saturated fats, which are typically animal fats, semisolid to solid at room temperature. Unsaturated fats are typically vegetable oils, liquid at room temperature.

Generally speaking the saturated fats are the bad ones that are involved in the development of diseases such as atherosclerosis, heart disease and cancer. The unsaturated fats, in unprocessed form and moderate amounts, are generally beneficial for health.

Plants and animals can make unsaturated fatty acids from saturated fats to an extent that the human body is incapable of. This ability enables plants to produce the essential omega-6 and omega-3 fatty acids linoleic and alpha-linolenic acid, which are vital to human health.

The "parent" of EFAs in the omega-6 family is linoleic acid (18:2w6). It has a chain of 18 carbon atoms, two double bonds, the first of which on the 6th carbon from the end, hence the name omega-6. This polyunsaturated fatty acid is abundant in safflower and sunflower oil, and is found to a lesser extent in sesame, corn and soybean oil. Its derivative gamma-linolenic acid (GLA, 18:3w6) is found in borage oil, hemp oil and evening primrose oil and has been the focus of research for a couple of decades.

The omega-3 family parent is alpha-linolenic acid (18:3w3), which has three double bonds with the first one in the 3-position. This family is sometimes called

lower in the DHA group, which indicates beneficial changes in renal function.

These experimental blood pressure lowering effects on rats have been confirmed in clinical trials on humans. Mori et al. (1999) conducted an interesting, double-blind, placebo-controlled trial with 59 overweight, hyperlipidemic men to compare the effects of purified EPA, DHA and olive oil supplementation (4g/d in capsules). Only DHA had significant blood pressure and heart rate lowering effects. Systolic and diastolic blood pressure fell on average 5.8 and 3.3 mmHg respectively, and daytime heart rate fell 3.7 bpm. These results also show that DHA, rather than EPA, is the principal omega-3 fatty acid in fish and fish oils responsible for their beneficial effects on the cardiovascular system.

The beneficial effects of the omega-3 fatty acids EPA and DHA had previously been attributed mainly to EPA because of its predominance in fish oil. However, it has recently become clear that DHA is the more important of the two. For example, in comparison to EPA, DHA has consistently proven to be more effective in lowering plasma triglycerides, increasing HDL cholesterol levels and lowering blood pressure and heart rate, while also being unique in its effect on the central nervous system.

In another randomized clinical trial a combination of highly purified DHA and EPA significantly reduced blood pressure in mildly hypertensive men (Prisco et al, 1998). Daily supplementation with 1.4 g DHA and 2.04 g EPA resulted in a decrease in both systolic (6 mmHg) and diastolic (5 mmHg) blood pressure after two months. No further effect was observed at four months and there was a return to baseline levels after two months without supplementation.

Serum lipids (Cholesterol and triglycerides)

GLA and DHA have repeatedly shown a remarkable effect on the reduction of cholesterol and triglyceride levels in both animal and human studies.

#### Cutting Edge Research on PPAR-RXR

"The discovery that some fatty acids can act as hormones, by binding to and activating nuclear factors, and thus regulate cellular and physiological pathways at the transcriptional level, emphasizes that fatty acids are not just passive energy-providing molecules, but are active participants in metabolic regulation." (Wahli et al., 1999)

It would be only logical that fatty acids, being such essential molecules in our physiology, were closely regulated; that the body had sensors that could respond to changes in the available levels of fatty acid metabolites.

Very recently a regulatory system for the metabolism of fats was discovered. Peroxisome Proliferator-Activated Receptors (PPARs) were identified as nuclear hormone receptors, linking metabolism and gene expression. PPARs are transcription factors that regulate the expression of genes involved in fatty acid metabolism (Wahli et al., 1999). Not surprisingly, EFAs have been proven to play a key role in this regulatory system.

Polyunsaturated fatty acids, particularly EFAs and their metabolites have been found

In a clinical trial involving 12 hyperlipidemic men GLA supplementation of 240 mg/day was given for four months. The results demonstrated a significant average reduction of triglyceride levels (48%), most of which was achieved as early as four weeks after the start. Total cholesterol and LDL-cholesterol levels were significantly decreased, whereas the good HDL cholesterol was significantly increased (22%). (Guivernau et al., 1994).

While most studies of omega-3 supplementation have been done on men, an interesting study on the effects of omega-3 fatty acids on serum lipids in post-menopausal women was recently published (Stark et al., 2000). In this placebo-controlled, double-blind trial, 36 women received either omega-3 fatty acids (2.4 g/d EPA and 1.6 g/d DHA) or placebo oil. After 28 days of supplementation there was a marked reduction in serum triglycerides (26%) and a 28% lower ratio of triglycerides to HDL-cholesterol. Women with and without hormone replacement had the same results.

The long-term prevention of atherosclerosis does not, as we now know, depend entirely on lowering cholesterol and triglyceride levels, but rather on increasing the good HDL-cholesterol. Reduced incidence of cardiovascular disease has been observed in the presence of high HDL levels. Specific subfractions of HDL appear to be involved in this process.

A study on 350 men and women with normal blood pressure demonstrated an increase of HDL2, a particularly beneficial subgroup of HDL-cholesterol, particularly in women, when given omega-3 fatty acids for six months (Sacks et al., 1994).

superunsaturated to distinguish it from the polyunsaturated omega-6 family. Alpha-linolenic acid is found in flax, perilla, hemp and pumpkin seed oils as well as in canola and walnut oil. It is also found in green plants and micro-algae. Derivatives of this essential fatty acid include eicosapentaenoic acid (EPA, 20:5w3) and docosahexaenoic acid (DHA, 22:6w3). Both are found in cold-water fish, such as salmon, mackerel, herring and tuna that feed on DHA-rich micro-algae.

EFAs must be metabolized in several steps to express their full biological activity. Derivatives of linoleic acid are gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA) and arachidonic acid (AA), while alpha-linolenic acid converts to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Important enzymes are necessary for the conversion of the EFAs in a process of elongation and desaturation (removal of hydrogen atoms, creating additional double bonds). The first step in both these families requires the enzyme delta-6-desaturase (D6D). The metabolites will in turn with the help of the enzymes cyclo-oxygenase and lipoxygenase convert to eicosanoids: prostaglandins, thromboxanes and leukotrienes. These are substances that have a big impact on body function in general and on inflammatory activity in particular. We get bad or good effects depending on the kind of fat ingested and its related eicosanoid production (Leaf et al., 1988).



to be PPAR ligands, binding to and activating these nuclear receptors. The antidiabetic drugs, called glitazones or thiazolidinediones, act similarly as PPAR ligands (see text). It was originally demonstrated that PPAR is activated by fibrates, a group of lipid-lowering agents. Because fibrates and polyunsaturated fatty acids were known to possess similar activities, the attention of researchers turned to fatty acids. Forman et al. (1997) discovered that GLA, DHA and other EFAs are efficient activators of PPAR $\alpha$ .

To activate gene transcription, PPAR must combine with the retinoic X receptor (RXR) to form the heterodimer PPAR-RXR. RXR is the receptor for a vitamin A metabolite (9-cis-retinoic acid), and has recently been identified as a cofactor for efficient gene expression activated by many other members of the steroid and thyroid hormone receptor superfamily, including the PPAR, vitamin D, and thyroid hormone receptors. A research team investigating brain tissue from mice last year identified an RXR-activating factor that turned out to be DHA (Mata de Urquiza et al., 2000). DHA binds directly to RXR, and like the other EFAs known to bind to PPAR, it is likely to express many of its beneficial effects through the PPAR-RXR heterodimer. This discovery suggests that DHA influences neural function through activation of an RXR-signaling pathway.

The new awareness of the PPAR-RXR system and its ligands makes the powerful influence of EFAs on the organism more understandable, and encourages further research on the details of how to use EFAs in prevention and treatment of our most feared diseases.

The effects of GLA on subfractions of HDL were studied in rabbits due to their similarity of plasma lipoprotein to humans (Fragoso et al., 1992). After four weeks of GLA supplementation there were no changes in the total cholesterol and triglyceride levels, but large changes in the distribution of HDL subfractions. A relative increase in the proportion of HDL2b and HDL3c was observed, an alteration that returned to basal levels 12 weeks after GLA withdrawal. This is especially noteworthy since the HDL2b subfraction is increased in centenarians as compared to both 'middle-aged' and 'elderly' subjects according to a study on long-lived individuals conducted by Barbagallo et al. (1998). In the same study HDL2b was also found to be inversely correlated with coronary heart disease and therefore likely to favor healthy aging.

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### Stress and behavior

Repeated exposure to psychosocial stressors as well as exaggerated reactivity to stress have been implicated as factors in the development of hypertension and heart disease. In addition, chronically elevated levels of stress-related hormones (catecholamines and glucocorticoids) are known to inhibit the activity of D6D, the enzyme needed for metabolism of EFAs.

Several early studies on rats found that dietary omega-6 and omega-3 fatty acids reduced the cardiovascular reaction to stress (Mills et al., 1985, 1986). Hence it is not surprising that both GLA and DHA have been found to reduce blood pressure and heart rate responses to psychosocial stress in humans.

Mills extended his findings to humans in a four-week study on 30 male university students (1989). Three different treatment groups were given either borage oil (1.3g/d), fish oil (1.6 g/d) or olive oil (as placebo). Borage oil significantly reduced stress-induced systolic blood pressure and heart rate after four weeks of supplementation, whereas olive oil and fish oil were without effect. Task performance was also significantly improved in the borage oil group, while un-changed by olive oil and fish oil, in a test that required a high level of attention and was designed to measure the cardiovascular response to psychological stress.

These results were similar to findings in the earlier animal studies and suggest that borage oil supplementation is effective in reducing cardiovascular reactions to stressors of all kinds, of both short and long-term, psychological and physical nature.

As a follow-up to earlier findings that DHA intake prevents aggression from increasing at times of mental stress (Hamazaki et al., 1996) Sawazaki et al. (1999) conducted an excellent double-blind study to test the effect of DHA intake on the level of stress hormones (epinephrine and norepinephrine). Fourteen medical students were studied over a stressful nine-week period when they underwent over 20 final exams. The participants in the DHA group were given 1.5 g DHA/day, while the control group members were given a mix of plant oils, all in capsules taken with meals.

The norepinephrine levels were high in both groups at the beginning of the study, since the students had already been under stress for some time, preparing for the exams. At the end of the test period the DHA group showed significantly reduced (-31%) norepinephrine levels, which is believed to be protective and beneficial for the cardiovascular system. In the control group the norepinephrine levels were still high. Epinephrine and cortisol showed no significant changes in either group. (Elevated norepinephrine levels are associated with chronic stress, while epine-phrine increases in situations of acute "survival" stress).

Similar findings of reduced norepinephrine levels related to EFA intake have been reported by other authors (Singer et al., 1990; Christensen et al., 1994). In Singer's study on 47 hypertensive individuals, norepinephrine levels were reduced 80% after treatment with omega-3 fatty acids compared to the control groups. Christensen's study showed that norepinephrine levels of men who died from cardiovascular disease were significantly higher than those of survivors.

Interestingly, the students in Awazaki's study were under considerable stress even long before the testing began, and the baseline levels of norepinephrine were already high at the start. This means that DHA was able to modulate catecholamine metabolism even after the appearance of stress. This is a noteworthy point when applying these results to daily life, as we usually do not try to counteract stress until after it starts.

### Insulin resistance

Insulin resistance is a common phenomenon in aging and in simple overweight. It is a primary factor in the so called metabolic syndrome X and is strongly linked to the development of a cluster of common age-related disorders including type 2 diabetes, obesity, hypertension, hyperlipidemia and heart disease. Insulin resistance is found in

### Fats & Fats

The fact that not all fats are equal was clearly brought to our attention through an epidemiological survey of chronic diseases in Greenland in 1950 to 1974. In spite of a diet very high in fats the Greenlanders had an extremely low frequency of both cardiovascular disease (~5%) and diseases such as diabetes, asthma, MS and psoriasis. What made such a difference in their disease spectrum compared to the high incidence (~50%) of these diseases in our country?

A primary factor turned out to be the kind of fatty acids in the fats consumed. The traditional food in Greenland comes to a large extent from fish and whales and contains a high percentage of essential fatty acids. In contrast, the average American diet, also high in total fat, is very low in essential fatty acids. Accordingly, a high fat diet is not necessarily bad, provided it contains a sufficient proportion of EFAs. Similarly, a low fat diet is not necessarily good if it does not provide the body with a sufficient amount of essential fatty acids. A fat-restricted diet will actually lead to an unwanted stimulation of lipid peroxidation and formation of pro-inflammatory substances, involved in the development of chronic degenerative diseases such as atherosclerosis and rheumatoid arthritis (Adam et al., 1995).

approximately 25% of apparently healthy humans.

Insulin resistance means that cells are desensitized to insulin signaling that normally leads to glucose uptake. The body tries to compensate for higher levels of circulating glucose by increasing insulin production. When this temporary compensatory mechanism fails, the glucose levels stay elevated, leading to diabetes and other degenerative complications.

Research has now shown a strong connection between the intake of essential fatty acids, in particular GLA and DHA, and improved insulin sensitivity (reduced insulin resistance).

Both human and animal studies show that a dietary intake of EFAs both increases the unsaturated fatty acids in membrane phospholipids and makes the individual more insulin sensitive (Storlien et al., 1986, 1987; Borkman et al., 1993; Vessby et al., 1994; Pan et al., 1995; Storlien et al., 1996).

Until recently, however, scientists did not understand the deeper mechanisms behind the influence of EFAs on insulin resistance. The discovery of a fundamental mechanism for the regulation of fat metabolism in the body has shed light on the effect of EFAs: the nuclear receptors and transcription factors called peroxisome proliferator-activated receptors or PPARs (See side bar on previous page).



Recently developed drugs, called glitazones or thiazolidinediones, that bind to and activate PPAR, increase insulin sensitivity. We now know that GLA and DHA, as well as certain other EFAs work in the same way, binding to and activating PPAR.

**DHA has been discovered to be of major importance for the development and maintenance of brain function, both in young and old individuals.**

#### Brain development and learning

In the last decade DHA has been discovered to be of major importance for the development and maintenance of brain function, both in young and old individuals. As the major structural and functional EFA of the central nervous system, including the retina of the eye (Connor et al., 1992), it constitutes as much as 30% to 50% of the total fatty acid content of the human brain and is essential for optimal neurological function. Part of the reason for this unique function is the role of DHA in the synthesis of phospholipids in nerve cell membranes.

Nothing can be more important than an adequate supply of DHA at the beginning of life, since it is essential for the growth and functional development of the brain in infants. DHA deficiencies in infancy have been associated with visual impairment and the later development of disorders including attention deficit hyperactivity disorder (ADHD), learning disabilities and aggressive behavior. DHA is also required for the maintenance of normal brain function in adults, for learning and for memory, and low levels have been shown to be a risk factor for Alzheimer's disease (Horrocks et al., 1999).

Many experimental studies on mice and rats have been conducted to clarify the effects of DHA on learning and memory. These studies clearly indicate that DHA deficiency is associated with a loss of discriminative learning ability (Greiner et al., 1999), while omega-3 enriched diets increase learning ability in elderly animals.

The Japanese research team Lim and Suzuki demonstrated superior maze-learning ability in old mice fed a DHA supplemented diet. After four months on the diet the mice

Not only do we need a sufficient amount of EFAs, however, we also need the right EFAs in a balanced proportion (see text). In short, we need to reduce the intake of omega-6 oils, except GLA, and increase omega-3 fatty acids, particularly DHA.

Our ancestors, being hunters and gatherers of plants, had a good source of essential fatty acids in their food. Wild game and free-range animals, cold-water fish, nuts and seeds provided a balanced mix of omega-3 and omega-6 fatty acids. Even today, the lowest rate of heart attacks in the world is found in island cultures, where the population still uses mainly unprocessed food from nature (Kagawa et al., 1982; Sandker et al., 1993).

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made significantly fewer mistakes and spent less time in the maze than the control group. They even performed better than the young rats on the control diet (Lim & Suzuki, 2000). When the re-searchers studied the relationship between the time of DHA intake and maze behavior, they found that an improved maze-learning ability was evident at one month after the feeding started, whereas increased DHA levels in the brain were apparent as early as two weeks. These results suggest that improvement in learning ability may take some time after the incorporation of DHA into the brain (Lim & Suzuki, 2001).

## Dementia

As we have seen, aging is often connected to a decreased meta-bolism of EFAs. Changes in the fatty acid composition of brain lipids during aging appear to be correlated with a deterioration of the central nervous system. Knowing that DHA constitutes a major portion of the fatty acids in the brain, it may not be surprising that low DHA levels are shown to be a significant risk factor for the development of Alzheimer's disease.

In a recent study tracking DHA levels in 1188 elderly American subjects for 10 years, Alzheimer's disease was 67% more likely to develop in individuals with DHA levels in the lower half of the distribution (Kyle et al., 1999).

Brain cholinergic systems are generally thought to be critical for memory function. Dysfunction of the central cholinergic system has been seen both in patients with vascular dementia and with senile dementia of Alzheimer's type. In a study on stroke-prone spontaneously hypertensive rats Minami et al. (1997) demonstrated that DHA increased choline and acetylcholine levels in the brain, while improving passive avoidance performance.

Interesting results from a Japanese clinical trial on DHA and dementia provide encouragement for further research. This pilot study involved 20 elderly people (average 83 years) with moderately severe dementia from thrombotic cerebrovascular disorder (stroke) (Terano et al., 1999). The participants all lived in the same home for the elderly and ate the same food. They were divided into two groups according to age and baseline scores on psychometric tests. The individuals in the treatment group received 720 mg of DHA daily for one year. Significant improvement in the dementia scores was noticeable after three to six months of DHA supplementation. The control group showed no improvement.

## Safety

With all these benefits of GLA and DHA in mind it is important to remember that too much of a good thing is not always good. Balance is the key, in this case between omega-6 and omega-3 fatty acids. The easiest and safest way to accomplish this balance is by taking a high quality combination supplement (ideally in the 2:1 range), while reducing dietary intake of saturated and hydrogenated fats.

Through the simple and safe procedure of supplementing our diet with a balanced combination of GLA and DHA it seems evident from current research that we have the chance to prevent a significant portion of the age-related degenerative diseases that plague our society today. It will ease our bodies' response to stress and may even help us to escape dementia.

### Omega-6 Oils In The Grocery Store

Even the right kinds of fats, when processed in the wrong way will cause degenerative effects. This is unfortunately the case with many omega-6 oils, including safflower, sunflower, sesame and corn oils. These oils have been popular and in demand for quite a few years. In their natural unprocessed state these oils are good for us in moderate amounts. Unfortunately, due to their double bonds, they are unstable and vulnerable to heat and light and quickly go rancid from lipid peroxidation. Therefore, most of these oils are processed to increase shelf life. In this process (hydrogenation and trans-configuration; see side bar on previous page) they lose their beneficial effects, behave like saturated fats and make matters even worse by inhibiting the incorporation of good EFAs into cell membranes.

Hydrogenation is a drastic but common way of changing natural oils to more solid fats with longer shelf life and profoundly altered biochemical properties. Valuable EFAs are destroyed by trans-fatty acid production and saturation with hydrogen.

In this process hydrogen gas is bubbled through the heated oil in the presence of a nickel catalyst. Double bonds are either saturated or turned from cis- to trans-configuration. Trans-fatty acids are produced through rotation of the molecule in high temperature around the double bonds, flipping the hydrogen atoms on the carbons involved onto the opposite side of the molecule.

Trans-fatty acids have many detrimental effects on the body due to the fact that they act as antagonists to essential fatty acids and interfere with the production of good prostaglandins. It has been shown in some studies that trans-fatty acids increase total cholesterol and LDL cholesterol even more than saturated fats. Partially hydrogenated products rich in trans-fatty acids are margarines, shortenings and hydrogenated oils.

For cooking the best oils are canola and olive oil. These oils are composed mainly of the monounsaturated oleic acid and are therefore more stable than the unsaturated oils.

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## References

- Barbagallo CM et al.: Lipoprotein profile and high-density lipoproteins: subfractions distribution in centenarians. *Gerontology* 1998; 44(2):106-10.
- Biagi PL et al.: Gamma-linolenic acid dietary supplementation can reverse the aging influence on rat liver microsomal delta 6-desaturase activity. *Biochim Biophys Acta*. 1991; 1083(2):187-92.
- Birch EE et al.: A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Dev Med Child Neurol*. 2000; 42(3):174-81.
- Bolton-Smith C et al.: Evidence for age-related differences in the fatty acid composition of human adipose tissue, independent of diet. *Eur J Clin Nutr*. 1997; 51(9):619-24.
- Borkman M, Storlien LH et al.: The relation between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids. *N Engl J Med*. 1993; 328(4):238-44.
- Christensen NJ et al.: Resting venous plasma adrenalin in 70-year-old men correlated positively to survival in a population study: the significance of the physical working capacity. *J Intern Med*. 1994; 235(3):229-32.
- Daviglus ML et al.: Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med*. 1997; 336(15):1046-53.
- de Urquiza AM et al.: Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. *Science*. 2000; 290(5499):2140-4.
- Engler MM: Comparative study of diets enriched with evening primrose, black currant, borage or fungal oils on blood pressure and pressor responses in spontaneously hypertensive rats. *Prostaglandins Leukot Essent Fatty Acids*. 1993; 49(4):809-14.
- Engler MM et al.: Dietary gamma-linolenic acid lowers blood pressure and alters aortic reactivity and cholesterol metabolism in hypertension. *J Hypertens*. 1992; 10(10):1197-204.
- Engler MM et al.: Effects of dietary gamma-linolenic acid on blood pressure and adrenal angiotensin receptors in hypertensive rats. *Proc Soc Exp Biol Med*. 1998; 218(3):234-7.
- Engler MM et al.: Docosahexaenoic acid is an antihypertensive nutrient that affects aldosterone production in SHR. *Proc Soc Exp Biol Med*. 1999; 221(1):32-8.
- Fardella CE et al.: Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. *J Clin Endocrinol Metab*. 2000; 85(5):1863-7.
- Forman BM et al.: Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. *Proc Natl Acad Sci U S A*. 1997; 94(9):4312-7.
- Fragoso YD et al.: The effect of gamma-linolenic acid on the subfractions of plasma high density lipoprotein of the rabbit. *Biochem Pharmacol*. 1992; 44(6):1085-90.
- Greiner RS et al.: Rats with low levels of brain docosahexaenoic acid show impaired performance in olfactory-based and spatial learning tasks. *Lipids*. 1999; 34 Suppl:S239-43.
- Guivernau M et al.: Clinical and experimental study on the long-term effect of dietary gamma-linolenic acid on plasma lipids, platelet aggregation, thromboxane formation, and prostacyclin production. *Prostaglandins Leukot Essent Fatty Acids*. 1994; 51(5):311-6.
- Hamazaki T, Sawazaki S et al.: The effect of docosahexaenoic acid on aggression in young adults. A placebo-controlled double-blind study. *J Clin Invest*. 1996; 97(4):1129-33.
- Hamazaki T, Sawazaki S et al.: Administration of docosahexaenoic acid influences behavior and plasma catecholamine levels at

times of psychological stress. *Lipids*. 1999; 34 Suppl:S33-7.

Horrobin DF: Loss of delta-6-desaturase activity as a key factor in aging. *Med Hypotheses*. 1981; 7(9):1211-20.

Horrobin DF: The regulation of prostaglandin biosynthesis by the manipulation of essential fatty acid metabolism. *Rev Pure Appl Pharmacol Sci*. 1983; 4(4):339-83.

Horrobin DF.: Fatty acid metabolism in health and disease: the role of delta-6-desaturase. *Am J Clin Nutr*. 1993; 57(5 Suppl):732S-736S.

Horrocks LA and Yeo YK: Docosahexaenoic acid-enriched foods: production and effects on blood lipids. *Lipids*. 1999; 34 Suppl:S313.

Horrocks LA, Yeo YK: Health benefits of docosahexaenoic acid (DHA) *Pharmacol Res*. 1999; 40(3):211-25.

Khalilov EM et al.: Omega-6 and omega-3 polyunsaturated fatty acids in experimental atherosclerosis regression. *EFA & Eicosanoids* 1997, Edinburgh.

Kimura S et al.: Dietary docosahexaenoic acid (22:6n-3) prevents the development of hypertension in SHRSP. *Clin Exp Pharmacol Physiol*. 1995; 22 Suppl 1:S308-9.

Kyle DJ et al.: Low serum docosahexaenoic acid is a significant risk factor for Alzheimer's dementia. *Lipids*. 1999; 34 Suppl:S245.

Lim SY and Suzuki H: Intakes of dietary docosahexaenoic acid ethyl ester and egg phosphatidylcholine improve maze-learning ability in young and old mice. *J Nutr*. 2000; 130(6):1629-32.

Lim SY and Suzuki H: Changes in Maze Behavior of Mice Occur after Sufficient Accumulation of Docosahexaenoic Acid in Brain. *J Nutr*. 2001; 131(2):319-324.

Mills DE et al.: Gamma linolenic acid attenuates cardiovascular responses to stress in borderline hypertensive rats. *Lipids*. 1985; 20(9):573-7.

Mills DE et al.: Effects of essential fatty acid administration on cardiovascular responses to stress in the rat. *Lipids*. 1986; 21(2):139-42.

Mills DE et al.: Dietary fatty acid supplementation alters stress reactivity and performance in man. *J Hum Hypertens*. 1989; 3(2):111-6.

Mills DE and Ward Ron P: Dietary n-6 and n-3 Fatty Acids and Stress-induced Hypertension. *Pathophysiology and Roles in Clinical Medicine* 1990; pp 145-156.

Minami M et al.: Dietary docosahexaenoic acid increases cerebral acetylcholine levels and improves passive avoidance performance in stroke-prone spontaneously hypertensive rats. *Pharmacol Biochem Behav*. 1997; 58(4):1123-9.

Mori TA et al.: Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension*. 1999; 34(2):253-60.

Pan DA et al.: Skeletal muscle membrane lipid composition is related to adiposity and insulin action. *J Clin Invest*. 1995; 96(6):2802-8.

Prisco D et al.: Effect of medium-term supplementation with a moderate dose of n-3 polyunsaturated fatty acids on blood pressure in mild hypertensive patients. *Prostaglandins Leukot Essent Fatty Acids*. 2000; 62(2):129-34.

Sawazaki S et al.: The effect of docosahexaenoic acid on plasma catecholamine concentrations and glucose tolerance during long-lasting psychological stress: a double-blind placebo-controlled study. *J Nutr Sci Vitaminol (Tokyo)*. 1999; 45(5):655-65.

Singer P et al.: Effects of dietary oleic, linoleic and alpha-linolenic acids on blood pressure, serum lipids, lipoproteins and the formation of eicosanoid precursors in patients with mild essential hypertension. *J Hum Hypertens*. 1990; 4(3):227-33.

Stark KD et al.: Effect of a fish-oil concentrate on serum lipids in postmenopausal women receiving and not receiving hormone replacement therapy in a placebo-controlled, double-blind trial. *Am J Clin Nutr*. 2000; 72(2):389-94.

Storlien LH et al.: Fat feeding causes widespread in vivo insulin resistance, decreased energy expenditure, and obesity in rats. *Am J Physiol*. 1986; 251(5 Pt 1):E576-83.

Storlien LH et al.: Fish oil prevents insulin resistance induced by high-fat feeding in rats. *Science*. 1987; 237(4817):885-8.

Storlien LH et al.: Dietary fats and insulin action. *Diabetologia* 1996; 39(6):621-31.

Terano T et al.: Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. *Lipids*. 1999; 34 Suppl:S345-6.

van Jaarsveld PJ et al.: The influence of different ratios and dosages of an w6:w3 fatty acid supplement on the lipoprotein cholesterol and fatty acid profile in nonhuman primates on a Western atherogenic diet. *Nutrition Research* 1997; 17 (11/12):1733-1747.

Venter CP et al.: Effects of essential fatty acids on mild to moderate essential hypertension. *Prostaglandins Leukot Essent Fatty Acids*. 1988; 33(1):49-51.

Vessby B et al.: Insulin sensitivity is related to the fatty acid composition of serum lipids and skeletal muscle phospholipids in 70-year-old men. *Diabetologia*. 1994; 37(10):1044-50.

Wahli W et al.: Fatty acids, eicosanoids, and hypolipidemic agents regulate gene expression through direct binding to peroxisome proliferator-activated receptors. *Adv Exp Med Biol*. 1999; 447:199-209.

Weber KT: Aldosterone and spironolactone in heart failure. *N Engl J Med*. 1999; 341(10):753-5.

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