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## LOOKING AHEAD

*There is compelling epidemiological evidence that low dietary intake of the omega-3 fatty acids EPA and DHA is positively related to rates of major depression.*

# Fatty Acid Facts, Part I. Essential Fatty Acids as Treatment for Depression, or Food for Mood?\*

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by Ernest K.J. Pauwels and  
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In recent decades, depressive disorders have reached an epidemic nature. The World Health Organization has predicted that by 2020 clinical depression will be the number two disabling disease worldwide, second only to cardiovascular disease. It is not likely that this increase finds its origin in improved diagnostic methods and higher awareness of health professionals.<sup>1</sup> At present, the increased prevalence is explained by a multitude of determinants, including non-Mendelian and environmental factors. With regard to the latter, our rapidly changing lifestyle is thought to be of major influence. This has prompted research into dietary habits which may make an etiological contribution to mood disorders. In the 20th century, one clear change in diet of the population of developed countries has been the replacement of omega-3 polyunsaturated fatty acids from fish and wild game with saturated fats and trans-fats

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### Summary

The epidemic character of depressive disorders has prompted further research into dietary habits that could make an etiological contribution. One clear change in the diet of the population in developed countries has been the replacement of omega-3 polyunsaturated fatty acids by saturated fats and trans-fats as well as by omega-6 polyunsaturated fatty acids. Omega-3 and omega-6 fatty acids are essential fatty acids, and the members of the -3 and -6 series are crucial for human health. In biochemical processes there is a competition between these two series. A higher dietary intake of omega-6 results in the excessive incorporation of these molecules in the cell membrane with numerous pathological consequences, presumably due to the formation of proinflammatory eicosanoids. Members of the omega-3 family and their derivatives modulate the inflammatory action. Essential fatty acids play a major role in brain development and brain functioning. The omega-3 series members docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) provide fluidity to the cell membrane, facilitating certain processes including neurotransmission and ion channel flow. It is thought that omega-3 deficiency during the fetal and postnatal period may have a long-term effect at various levels. Epidemiological studies have demonstrated a positive association between omega-3 deficits and mood disorders. As for treatment, there is convincing evidence that add-on omega-3 fatty acids to standard antidepressant pharmacotherapy results in improved mood. There is no evidence that fatty acid monotherapy has a mood-elevating effect, with a possible exception for childhood depression. There are indications that omega-3 has a prophylactic effect on perinatal depression and has a negative effect on natural killer cell activity and T-lymphocyte function. These observations need further study in view of the popularity of self-medication. © 2008 Prous Science, S.A.U. or its licensors. All rights reserved.

as well as with omega-6 polyunsaturated fatty acids from other food sources. Particularly, the increased consumption of naturally occurring omega-6 fatty acids provided good grounds for the hypothesis that proin-

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\*Dedicated to Prof. Pauwels' friend Dr. Erik L. Noach, emeritus professor of Pharmacology at Leiden University, who taught him the principles of neurotransmission in the early 1970s.

**BOX 1.**

Most fats have a basic chemical structure consisting of one or more fatty acids covalently bound to an alcohol via an ester bond. Fatty acid molecules consist of a hydrocarbon chain with a carboxylic group at the end while natural fatty acids contain an even number of carbon atoms. In addition, saturated fatty acids contain no double bonds in their chemical structure, whereas unsaturated fatty acids do. In biological structures, fatty acids usually contain 10–26 carbon atoms, and C16, C18 and C20 fatty acids are abundant. The methyl end of the molecule is designated as the omega-carbon. Unsaturated fatty acids are classified according to the position of the first double bond. In this way, the omega-3 fatty acids have a double unsaturated bond at the third carbon atom. Likewise, the omega-6 fatty acids have their double bond at the sixth carbon. In this paper the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are important.

DHA has a 22 carbon-chain with 6 polyunsaturated bonds. It is designated as a 22:6, omega-3 fatty acid. In the same way, EPA is designated as a 20:5, omega-3.

Essential fatty acids (EFAs) are essential to human health, but cannot be made in the body and must therefore be obtained from our diet. There are two series of EFAs: the omega-3 series and the omega-6 series. The omega-3 series derives from  $\alpha$ -linolenic acid and the omega-6 series from linoleic acid. These two series of molecules are metabolized by the same set of enzymes, and all members of these families belong to the group of compounds named polyunsaturated fatty acids.

Fatty acids are building blocks of membrane phospholipids of all cells. In addition, these molecules are important for the vascular endothelium. Depletion of these compounds gives rise to vascular dysfunction, notably vascular inflammatory processes. EPA and DHA also modulate gene expression and repression regulating metabolic processes as well as mechanisms of neurotransmission. As for the brain, dietary deficiency in these fatty acids is associated with psychiatric diseases and cognitive impairment.

In biochemical processes, a competition exists between omega-3 and omega-6 fatty acids. A higher dietary intake of omega-6 fatty acids results in the incorporation of these molecules in cell membranes with numerous pathological consequences, such as cardiovascular disease, neuropsychiatric disorders and inflammation-related diseases such as rheumatoid arthritis, diabetes mellitus and hypertension. These types of diseases find their origin in the production of proinflammatory eicosanoids from omega-6 fatty acids and—to a far lesser degree—from omega-3 fatty acids. Prostaglandins, thromboxanes, lipoxins and leukotrienes belong to the family of eicosanoids. These molecules are created in the cell and serve as “local hormones,” important for fundamental processes such as the transport of ions and molecules in and out of the cell, vascular tone, thrombogenesis, inflammation and cell division and growth. Many types of eicosanoids work together in biochemical networks of loops and feedback processes.

flammatory molecules play a role in the increasing prevalence of depression (see Box 1).

Intriguing results have been obtained from epidemiological studies demonstrating a link between low or moderate intake of omega-3 fatty acids and mood disorders.<sup>2,3</sup> However, not all studies are unanimously positive and also results showing no association between dietary omega-3 fatty acid intake and low mood levels have been reported.<sup>4,5</sup> Nevertheless, the far majority of case, cohort and population studies associating omega-3 intake with mood disorders provide a positive link. Furthermore, the importance of this research field is illustrated by the large number of ongoing and already published governmentally supported trials.<sup>6</sup> Of special interest are trials designed to test the efficacy of omega-3 fatty acid intervention, either by monotherapy or as augmentation to standard pharmacotherapy for mood disorders.<sup>7</sup>

The current review focuses on the effects of polyunsaturated fatty acids—

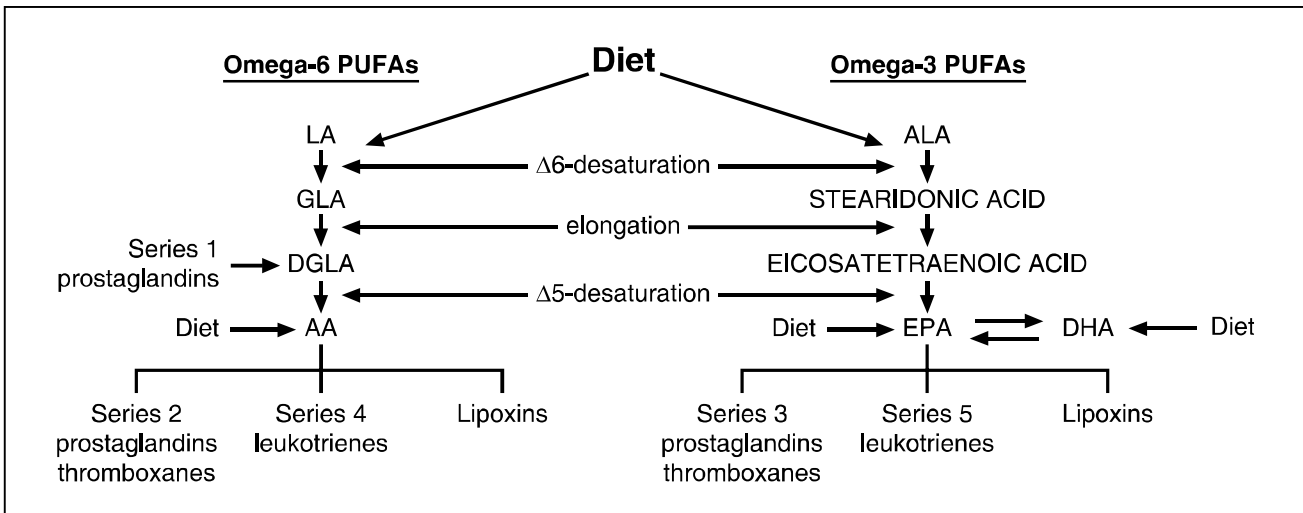
notably, omega-3 fatty acids—and their metabolic derivatives on depressive disorders. This paper discusses the clinical investigations in this area in light of the molecular mechanisms of fatty acids with regard to brain development and functioning.

### **Biochemical and biological aspects of essential fatty acids**

$\alpha$ -Linolenic acid (ALA) is the molecule from which the omega-3 series of polyunsaturated fatty acids is derived. The omega-6 series is derived from *cis*-linoleic acid (LA). Both series of essential fatty acids (EFAs) use the same set of enzymes for their metabolic pathways, although the enzymatic reactions display a higher efficiency for omega-3 fatty acids. Dietary LA and ALA are metabolized by  $\Delta 6$  desaturase (D6D) and  $\Delta 5$  desaturase (D5D), during which process two hydrogen atoms are removed. Elongase enzymes add two carbon atoms to form 20-carbon triple saturated fatty acids. This way, in the omega-3 series eicosapentaenoic acid (EPA) is formed. Likewise, arachidon-

ic acid (AA) results from enzymatic processes in the omega-6 series. Mammalian cells lack both the D5D and D6D enzymes and must obtain the long-chain EFAs from dietary intake. Whereas omega-6 family members are abundantly available in our food, omega-3 family members are more difficult to obtain, although they are essential for a proper biological functioning of the body.<sup>8</sup> Various exogenous factors affect these enzymatic processes in the omega-3 and -6 series. Alcohol, glucose, saturated fats and cholesterol inhibit desaturase activity, mostly D6D. Under disease conditions such as diabetes mellitus, infection, hypertension and hyperthyroidism, D5D and D6D actions are also diminished.

Mental depression and atherosclerotic diseases may be chronic inflammatory processes.<sup>9</sup> As EPA and its daughter molecule docosahexaenoic acid (DHA) produce inflammation-modulating substances, the beneficial effects of these fatty acids on these diseases are thought to originate from this action.<sup>9</sup> Saturated fatty acids interfere with the enzymatic production of EPA



**Fig. 1.** Simplified scheme of essential fatty acid metabolism of the omega-3 and omega-6 series. PUFA, polyunsaturated fatty acid; LA, linoleic acid (18:2n-6); ALA,  $\alpha$ -linolenic acid (18:3n-3); GLA,  $\gamma$ -linolenic acid (18:3n-6); DGLA, dihomogamma-linolenic acid (20:3n-6); AA, arachidonic acid (20:4n-6); EPA, eicosapentaenoic acid (20:5n-3); DHA, docosahexaenoic acid (22:6n-3).

and DHA (and other EFAs in the omega-3 family), which could explain their role in the genesis of mental and vascular disorders, often considered related clinical conditions.<sup>10</sup> Also, molecules in the omega-6 series are involved in inflammatory processes. Metabolic pathways in this series result in the production of proinflammatory eicosanoids of the -2 series from AA (see Fig. 1). The -2 series of prostaglandins originates from the root compound AA and include prostaglandin A<sub>2</sub> (PGA<sub>2</sub>), PGD<sub>2</sub>, PGE<sub>2</sub> and thromboxanes such as TXA<sub>2</sub> as well as leukotrienes of the -4 series. By contrast, inflammation-modulating prostaglandins of the -1 series are formed from dihomogamma-linolenic acid in the omega-6 pathway and prostaglandins of the -3 series and leukotrienes of the -5 series are formed from EPA. In addition, from both the omega-6 and the omega-3 family members other antiinflammatory molecules such as lipoxins, resolvins and protectins are formed.<sup>11</sup> Thus, interestingly, the biochemical pathways of EFAs result in both pro- and antiinflammatory molecules.<sup>12</sup> It is important to note that both EPA and DHA can replace omega-6 fatty acids, notably AA, in the cell membrane of most tissues. This maintains the membrane integrity and fluidity by phospholipid movements, which is impor-

tant for the selective transport of biomolecules. As for the brain, membrane fluidity determines the fidelity of the neurotransmission process. The replacement also reduces the release of proinflammatory molecules in the prostaglandin-2 series. The biosynthesis of eicosanoids and the mechanism of all those well-orchestrated processes is reviewed extensively in references.<sup>13-15</sup> The relationship between EFAs and inflammatory diseases has been reviewed in reference.<sup>16</sup>

### Fatty acids and brain development and functioning

The most abundant EFA in the brain is DHA. In the fetal period the maternal flow of DHA to the fetus occurs via transport proteins, of which  $\alpha$ -fetoprotein is the most important. In the postnatal period, DHA is provided to the infant in mother's milk. Formula-fed infants show less mature neurophysiological features and cognitive function than breastfed infants. However, supplementation with DHA and AA results in similar visual and IQ maturation between formula-fed and breast-fed infants.<sup>17</sup> These findings provide strong evidence that DHA is important for brain development.

The role of DHA in the developing brain has been attributed to major

functions of this fatty acid. DHA provides flexibility to the cellular membrane. As mentioned above, the membrane fluidity is important for intercellular signal transduction and neurotransmission. Further, the lipid profile of the membrane has an impact on ion channel activity, second messenger generation and gene expression.<sup>18</sup> Another feature of DHA in the brain appears to be its ability to scavenge free radicals. The molecule neuroprotectin D1 is derived from DHA and is known to protect retinal pigment epithelium. It also protects brain lipids and proteins against oxidative stress and regulates neuronal apoptosis. This property of DHA is of special interest in situations of ischemic brain disease and neurodegeneration.<sup>19</sup> Other recent investigations have emphasized the role of DHA in morphological differentiation of hippocampal neurons by increasing the population with more branches and longer neurites.<sup>20</sup>

In short, dietary omega-3 fatty acid intake, in particular DHA, has shown a remarkable influence on brain structure, development and function. DHA deficiency during the fetal period and postnatal period may have a long-term effect at various levels and long-term consequences for mental skills and the risk of neurodegenerative disorders throughout life.

## Epidemiological evidence

Around the turn of the century, various papers were published dealing with the association between severity of depression and levels and ratios of omega-6 and omega-3 fatty acids.<sup>21–23</sup> These papers coincided with the first reports on the strong negative correlation between fish consumption and depression. An unexpected low prevalence of winter depression among Icelandic people was attributed to a high consumption of fish<sup>24</sup> and could not be explained by average daylight availability.<sup>25</sup> In a study sample of 3204 Finnish adults, the likelihood of having depressive symptoms was significantly higher among infrequent fish consumers than among frequent consumers.<sup>26</sup> Also in Finland, the 1966 Birth Cohort Study ( $n = 5689$ ) provided a statistically significant association between low-frequency fish consumption and depression in women, but not in men.<sup>2</sup> Recently, the SUN cohort prospective study involving 7903 participants demonstrated a potential benefit of omega-3 fatty acid intake on mental disorders, including depression.<sup>3</sup> Another recent study reported on a subsample of the French SU.VI.MAX study investigating the influence of habitual fatty fish intake or omega-3 supplementation on mood. These investigators found a decrease of the risk of recurrent depression in nonsmokers. (By contrast, smokers eating fatty fish had an increased risk of recurrent depression.)<sup>27</sup>

An interesting article by McGrath-Hanna et al.<sup>28</sup> dwells on the changing diet of circumpolar people. Generational changes from fish and fish-based meals to a diet consisting of processed foods common in modern stores were accompanied by increased health problems, including a decline in mental health characterized by increased rates of depression, anxiety and suicide. (This alarming phenomenon has urged scientists and health policy makers to develop a support program to address these health challenges).<sup>29</sup>

The results of the above-mentioned observational studies are con-

trasted by a negative report by Hakkarainen et al.<sup>4</sup> from a nested study on cancer prevention with antioxidants. In a group of 29,133 male Finnish smokers followed during 9 years, the dietary intake of omega-3 fatty acids had no positive impact on self-reported low mood level. Interestingly, the group of participants with depressed mood was relatively large, amounting to 8612 subjects. However, the study did not take into account the fact that tobacco use decreases omega-3 long-chain fatty acid concentration in blood and that the antioxidant status of the participants may counteract the effects of fatty acid intake.<sup>30</sup>

In summary, there is increasing evidence of a positive association between omega-3 deficits and mood disorders. Recently, in a large observational study among 2982 participants this was, once more, confirmed by Appleton et al.<sup>31</sup> Although lifestyle factors may also contribute to depression, their findings suggest that higher levels of omega-3 EFA intake are associated with lower levels of depressed mood.

## Treatment studies

From a pharmacological standpoint, the observational studies mentioned above need to be confirmed by randomized, double-blind, placebo-controlled treatment trials. This is a proper approach to answering the question of whether omega-3 polyunsaturated fatty acids are effective in improving mood disorders, either by monotherapy or as augmentation to standard antidepressant therapy. With regard to monotherapy, Marangell et al.<sup>32</sup> studied 36 depressed patients randomly assigned to receive DHA or placebo. Their study failed to show any significant effect of DHA monotherapy. A most recent study among 190 participants suffering from mild to moderate depression was carried out in a double-blind randomized manner. Supplementation with EPA + DHA (1.5 g/day) had no beneficial (or harmful) effect on mood during the study period of 3 months.<sup>33</sup> On the other hand, Nemets et al.<sup>34</sup> reported on a

study with a combination of EPA and DHA (in a daily dose of 400 mg and 200 mg, respectively) in 28 patients aged 6–12 years suffering from childhood depression. Their study demonstrated a highly significant effect on depression scores and clinical symptoms.

A considerable number of randomized, placebo-controlled studies with add-on omega-3 fatty acids, notably EPA, has been performed and reported on. Improved mood as an effect of adding fish oil to existing therapy was found in various settings in published literature over the past decade (e.g., refs.<sup>35–38</sup>). Reviews and meta-analyses<sup>39,40</sup> of results from recent randomized, controlled trials unanimously reached positive conclusions in the sense that there is an overall significant antidepressant effect of add-on omega-3 fatty acids and that overall results are encouraging. Two very recent meta-analytical reviews deserve special attention: Lin et al.<sup>41</sup> and Montgomery and Richardson.<sup>42</sup> The former study pooled 10 double-blind, placebo-controlled studies in patients with mood disorders receiving omega-3 fatty acids. In the total number of 329 patients, a significant antidepressant effect ( $p = 0.003$ ) was found. In particular, omega-3 fatty acid treatment improved mood in patients with clearly defined depression ( $p = 0.002$ ) or with bipolar disorders ( $p = 0.0009$ ). The latter study selected five studies for their analytical review, but—due to variable methodological quality—only one study involving 75 patients was used for a final conclusion. The authors cautiously concluded that omega-3 fatty acids as an adjunctive treatment for depression but not for manic symptoms in bipolar disorders show positive effects. Both of these recent analyses observed publication bias and considerable heterogeneity in the available publications, and expressed the need for large-scale, well-designed treatment studies.

## Some considerations and conclusions

There is compelling epidemiological evidence that low dietary intake of

the omega-3 fatty acids EPA/DHA is positively related to rates of major depression. Furthermore, EPA/DHA augmentation with standard antidepressant therapy shows a beneficial effect. From a health perspective, this puts emphasis on the dietary omega-3/omega-6 balance, which has changed considerably in the 20th century from the presumably ideal ratio of 1:1 to less than 1:10. Diets in the Western world tend to have too much omega-6, principally due to consumption of animal meat.<sup>43</sup>

In view of the convincing epidemiological arguments, the question arises whether animal studies can support these findings. The forced swimming test in special laboratory rats has been used to evaluate changes in their characteristic immobile depression-like behavior. Other tests include the habitation in the open field and the maze performance of rodents. The available (but scarce) recent literature in this area suggests that impaired performance is linked to omega-3 fatty acid deficiency;<sup>43</sup> this finding supports the results of human studies. Moreover, animals that performed better in the swimming test had higher levels of DHA (50% increase), ALA (63% increase) in the brain and EPA (27% in the peripheral erythrocyte membrane).<sup>45</sup>

Although it appears that omega-3 fatty acids are a contributing factor to mood disorders, there are still issues that need clarification. To mention a few:

- Although it is likely that EFA monotherapy is ineffective, there might still be an effect in childhood depression. The intriguing result in this area<sup>35</sup> warrants further research, or at least clinical confirmation.
- Diminished natural killer cell action and T-lymphocyte proliferation have been reported in healthy subjects aged 55 years or more taking moderate amounts of EPA (720 mg/day).<sup>46,47</sup> This disturbing complication also requires further investigation, although a reassuring article on the effect on T lymphocytes and nat-

ural killer cell numbers in males aged 18–42 has recently been published.<sup>48</sup>

- The available literature regarding which fatty acid (EPA, DHA or both) is most effective at what dose in which disease (e.g., unipolar or bipolar depression, but also sleep disorders and anxiety) is not clear and requires further study.
- Would there be a prophylactic effect on perinatal depression that has a worldwide incidence of 10%? In a cross-national analysis, both higher seafood consumption and higher DHA content in mother's milk were predictive for a lower prevalence of postpartum depression.<sup>49</sup>
- It would be interesting to include nuclear medicine imaging in various studies. With appropriate radiolabeled ligands, SPECT and PET studies offer a unique way to evaluate effects in a quantitative manner.<sup>50</sup>

In view of the popularity of—often commercially stimulated—self-medication and the over-the-counter availability of EPA/DHA-enriched fish oil preparations, a few knowledge gaps still need to be resolved. This area represents an important, but rewarding, challenge for mental health researchers. After all, fish oil capsules are not bonbons.

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