THE POTENTIAL ROLE OF FATTY ACIDS IN ATTENTION-DEFICIT / HYPERACTIVITY DISORDER (ADHD)

A.J. Richardson[1,2] and B.K. Puri[1]

[1]MRI Unit, MRC Clinical Sciences Centre, Imperial College School of Medicine, Hammersmith Hospital, London W12 0HS, UK.

[2] University Department of Physiology, Oxford OX2 2PT, UK.

Correspondence to:

Dr. A.J. Richardson,
MRI Unit, MRC Clinical Sciences Centre,
Imperial College School of Medicine
Hammersmith Hospital,
Du Cane Road
London W12 0HS, UK

Telephone: 01865 513433
F*ax*: 01865 438433
E-mail: alex.richardson@physiol.ox.ac.uk

SUMMARY

As currently defined, attention-deficit hyperactivity disorder (ADHD) encompasses a broad constellation of behavioural and learning problems and its definition and diagnosis remain controversial. The aetiology of ADHD is acknowledged to be both complex and multifactorial. The proposal considered here is that at least some features of ADHD may reflect an underlying abnormality of fatty acid metabolism. Clinical and biochemical evidence is discussed which suggests that a functional deficiency of certain long-chain polyunsaturated fatty acids could contribute to many of the features associated with this condition. The implications in terms of fatty acid treatment proposals are also discussed; such a form of treatment is relatively safe compared to existing pharmacological interventions, although further studies are still needed in order to evaluate its potential efficacy in the management of ADHD symptoms.

INTRODUCTION

The cluster of age-inappropriate behavioural abnormalities of the triad inattention, hyperactivity, and impulsivity constitutes the core of the diagnostic group of disorders known as hyperkinetic disorder in the tenth revision of the International Classification of Diseases (ICD-10) (1), and known in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (2) as attention-deficit/hyperactivity disorder (ADHD). Clinically, there is impaired attention and overactivity, and both occur in more than one situation, for example at home, in school, or at a clinic. Impaired attention leads to frequent changes from one activity to another and unfinished activities. Overactivity manifests as excessive restlessness, for instance running and jumping around, noisiness, and excessive talkativeness. Associated features include disinhibition in social relationships, recklessness and the impulsive defying of rules.

In the UK hyperkinetic disorders are estimated around 1-2% of the population. The prevalence of ADHD in the US is around 30 to 50 per 1000 in school-age children. The much higher prevalence in America may be partly the result of differences in diagnosis. Although ADHD is often considered to be a disorder affecting children and adolescents, it is now clear that it can persist into adulthood.

The aetiology of ADHD is generally acknowledged to be multifactorial, involving both biological and environmental determinants. Increasingly, attention is being paid to the clinical heterogeneity of this disorder, with the aims of identifying both core and associated features, delineating possible subtypes, and clarifying the relationship of ADHD to other disorders.

In this paper we suggest that the study of fatty acid metabolism in relation to ADHD can play an important part in helping to elucidate these issues. There is considerable evidence that changes in dietary habits – and particularly the dramatic increase in the consumption of processed foods – have led to a situation in which relative deficiencies in certain essential fatty acids (EFAs) and their long-chain polyunsaturated fatty acid derivatives (LC-PUFAs) may be widespread in modern societies (3). The effects of reduced dietary intake on individuals will clearly depend on both constitutional and other environmental factors, but it is already acknowledged that these dietary changes have contributed to the increased incidence of many physical diseases, most notably cardiovascular disease. The issue of concern here, however, is the crucial importance of certain LC-PUFAs to the normal development and function of the brain, because substantial evidence is now emerging that fatty acid deficiencies may also play some part in a wide range of neurodevelopmental disorders, including ADHD.

In this paper we first present a brief overview of the importance of fatty acids in brain development and function. This is followed by a consideration of some of the clinical features associated with ADHD that are explicable in terms of fatty acid deficiency. It is emphasized that EFAs and their metabolites can have important psychopharmacological actions, such that an abnormality of fatty acid metabolism in ADHD in no way conflicts with current neurotransmitter models. Direct evidence for the involvement of fatty acid deficiencies in ADHD is then outlined.

Finally, preliminary evidence from treatment studies is considered.

We emphasize that the direct evidence for fatty acid deficiency as a factor in ADHD is still limited, and that it is too early to make any recommendations on the potential value of dietary supplements in the management of this condition. Nonetheless, there are very good grounds for taking seriously the hypothesis that deficiency in certain LC-PUFAs could be a contributory factor in at least a proportion of cases, and this has obviously raised the possibility of new therapeutic approaches. Although research in this area is only in its early stages, we feel that sufficient scientific evidence is already emerging to indicate that these issues deserve further systematic investigation.

THE IMPORTANCE OF FATTY ACIDS IN BRAIN DEVELOPMENT AND FUNCTION

Lipids have fundamental structural and functional rôles in the central nervous system. Neuronal membranes are largely made up of phospholipids, each containing two fatty acids. The phospholipid bilayer forms the matrix within which membrane proteins, such as receptors and ion channels, are embedded and to which membrane-associated proteins such as those involved in second messenger systems may be attached. The precise fatty acid composition of the membrane can affect the tertiary and quaternary structures of membrane-bound receptors and associated neurotransmitter functioning. In addition, most second messenger systems depend on lipids such as free fatty acids, diacylglyerols, prostaglandins, leukotrienes and hydroxy-fatty acids. Thus, fatty acids can profoundly influence key aspects of cell signalling (4-7).

Figure 1 shows the biosynthetic pathways for the major n-6 and n-3 fatty acids found in the mammalian central nervous system. The truly essential fatty acids (EFAs) which cannot be synthesized by the body and must therefore be provided in the diet are linoleic acid (n-6 series) and alpha-linolenic acid (n-3 series). The longer chain polyunsaturated fatty acids (LC-PUFAs) such as AA and DHA can usually be synthesized from these EFA precursors via processes of desaturation (insertion of a double-bond) and elongation (adding two carbon atoms to the fatty acid chain).

[Figure 1 approximately here]

Within the brain, four fatty acids are particularly important, as highlighted in Figure 1. They are arachidonic acid (AA) and dihomogamma linolenic acid (DGLA) from the n-6 series, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from the n-3 series. AA and DHA play a major structural rôle in neuronal membranes, making up 20 per cent of the dry mass of the brain. EPA and DGLA play a more minor structural rôle but are also crucial for normal brain function. Together with AA, these fatty acids are critically important as precursors of the eicosanoids (8), a complex group of highly biologically active compounds encompassing the prostanoids (including prostaglandins, thromboxanes and prostacyclins) and leukotrienes. Although very difficult to study *in vivo* owing to their predominantly local actions and short circulation time, these compounds are of great physiological importance as they perform numerous regulatory functions in the brain and throughout the rest of the body.

EFA metabolism can influence many aspects of brain development, including neuronal migration, axonal and dendritic growth, and the creation, remodelling and pruning of synaptic connections (9). Animal studies have shown that both neural integrity and function can be permanently disrupted by deficits of n-6 and n-3 fatty acids during fetal and neonatal development (10-12). While both n-6 and n-3 fatty acids are required, the n-3 fatty acids such as DHA appear to play a special rôle in highly active sites such as synapses and photoreceptors, and deficiencies have particularly been linked to visual and cognitive deficits (13,14). By contrast, deficiencies of AA have been associated more with reductions in general growth indices such as low birth weight and reduced head circumference.

Maternal fatty acid status during prenatal development thus appears to be an important issue, and there is considerable debate about whether preformed LC-PUFAs may be a requirement in very early life (15). There is evidence that infants may benefit from the LC-PUFAs that are naturally present in breast milk but absent from many formula feeds (16).

Adequate supplies of EFAs are also required throughout development and adult life in order to *maintain* normal function. As noted above, the truly essential fatty acids are linoleic acid (18:2 n-6) and alpha-linolenic acid (18:3 n-3), but it is their LC-PUFA derivatives that are most important in the brain. Unfortunately, various factors can interfere with the conversion of the parent EFAs to LC-PUFAs (17). These include:

- saturated or hydrogenated fats
- deficiency of vitamin and mineral cofactors (notably zinc deficiency)
- excessive alcohol consumption
- stress hormones

These potential blocks to conversion mean that a deficiency in LC-PUFAs such as AA and DHA can easily occur despite an availability of the EFA precursors in the diet.

Genetic as well as environmental factors are important. Via the efficiency of the enzyme systems involved, individuals differ in their *constitutional* ability to convert EFAs to LC-PUFAs, and inefficient conversion mechanisms would clearly increase the need for an adequate dietary intake of the preformed LC-PUFAs. This appears to be a factor in some atopic conditions (18,19), and in diabetes mellitus (20-22). Moreover, constitutional differences in EFA metabolism are increasingly recognized as a possible risk factor in a wide range of neurodevelopmental disorders (7, 9, 23).

Whether for environmental or genetic reasons, existing evidence suggests that impaired conversion of EFAs to LC-PUFAs may affect at least some individuals with ADHD, as discussed below.

THEORETICAL PLAUSIBILITY OF FATTY ACID DEFICIENCY AS A FACTOR IN ADHD

In the search for a neurochemical basis for ADHD, the emphasis has traditionally tended to be on neurotransmission. However, it is not widely appreciated that the functioning of neurotransmitters and their receptors can be profoundly influenced by the lipid environment. For example, *in vitro* experiments have shown that the efficacy of diazepam receptor binding can be approximately doubled by the introduction of just a single *cis* double bond into long-chain saturated fatty acids with chain lengths of 16-, 18-, or 20- carbon fatty acids (24,25). Both n-3 and n-6 PUFAs are implicated in many aspects of neurotransmitter metabolism and receptor function (4-7).

Insofar as some aspects of ADHD symptomatology may reflect dopaminergic abnormalities, it is notable that animal studies have shown that chronic n-3 PUFA deficiency is associated with decreased levels of endogenous dopamine and decreased D_2 receptor binding in frontal cortex (5). More detailed investigations suggest that n-3 deficiency reduces the vesicular storage of dopamine in frontal cortex (26), with suggestions that this inadequate storage may not be sufficient for the maintenance of high-release during stimulated cognitive processes. Moreover, behavioural effects of n-3 PUFA deficiency include changes in attention, motivation, and reactivity to stimuli and rewards, but not necessarily locomotion (27). It does not seem implausible that these kinds of observations may be relevant to ADHD, and perhaps to the distinction between Attention-Deficit Disorder with and without hyperactivity (28), but the studies necessary to evaluate this still remain to be carried out.

To take a much broader perspective, fatty acid deficiency as a contributory factor to ADHD could well help to account for a number of clinical observations and known associations. These are described in the following section.

CLINICAL FEATURES AND ASSOCIATED DISORDERS CONSISTENT WITH FATTY ACID DEFICIENCY

This section consists of brief consideration of various clinical features of ADHD which are difficult to explain on the basis of a neurotransmitter model. However, each observation is consistent with a model in which fatty acid deficiency is included as a potential contributory factor.

Sex ratio

It is well established that there is a higher prevalence of ADHD in males, with the ratio of males to females varying from 2:1 to 10:1 (29-31).

While difficult to explain on the basis of a neurotransmitter model, this clinical observation is readily explicable by a fatty acid model, as males are more vulnerable than females to LC-PUFA deficiency (32,33). A similar excess of males is found in other developmental disorders that show clinical and familial associations with ADHD and with each other, including dyslexia, dyspraxia, and schizophrenia, and there is evidence implicating abnormalities of fatty acid metabolism in these disorders (23, 34-40).

Minor physical abnormalities

ADHD is associated with an excess of minor physical abnormalities (41-43).

These are likely to involve abnormalities of cell remodelling, apoptosis and migration. Phospholipids, the EFAs and their metabolites play important rôles in these processes (44-46).

Sleep problems

Several studies have found children with ADHD to have a higher likelihood of sleeping problems than normal children, including difficulties in settling, night-time wakening and over-tiredness in the morning (47,48).

PUFAs have a pivotal rôle in the regulation of sleep mechanisms. They exert direct effects on neuronal membrane structure and indirect effects on the dynamics of compounds such as complex lipids, prostaglandins, neurotransmitters, amino acids and interleukins, that are necessary for the initiation and maintenance of normal sleep (49-50).

Allergies

The presence of chronic health problems, such as recurring upper respiratory problems, allergies or asthma, have been noted more often in hyperactive than in normal children (51-52).

In eczema and other atopic conditions, there is a reduction in the efficiency of the delta-6 desaturase enzyme, that is, problems in converting EFAs to LC-PUFAs (18, 19, 53).

Other somatic symptoms

Somatic complaints are more commonly reported in ADHD children compared with normal children (54). These typically include headaches, stomach-aches, proneness to infections and general malaise with no obvious cause. Thus Szatmari et al. (30) found that 24 per cent of ADHD boys and 35 per cent of ADHD girls between 12 and 16 years met the criteria for Somatization Disorder.

EFA deficiency is known to contribute to general health problems such as proneness to infections and digestive and related disorders, because LC-PUFAs and their derivatives play a crucial rôle in the regulation of immune and digestive functions (55-58).

Emotional and mood disorders

Comorbidity of ADHD with other behavioural and emotional disorders is common, with up to 44 per cent having at least one other psychiatric disorder (30). Symptoms of anxiety, depression, and low self-esteem are typical. A high rate of affective disorders has been found in both probands with

attention deficit disorders and in their relatives (59). Furthermore, two groups have reported an elevated risk of major depression during adolescence and young adulthood in ADHD subjects followed prospectively (60-62).

There is increasing evidence that n-3 fatty acid deficiency may be an important factor in clinical depression (63-67). Indeed, recently a preliminary double-blind, placebo-controlled trial has demonstrated the benefits of omega-3 fatty acids on the short-term course of illness in bipolar disorder (68).

Motor coordination problems and soft neurological signs

ADHD is frequently associated with poor motor coordination (51). Similarly, soft neurological signs, such as motor overflow movements, are also relatively common in ADHD (69,70).

Poor motor coordination is also compatible with EFA deficiencies, as movement disorders in the general population are associated with deficiencies in LC-PUFAs (71), as are the dyskinesias associated with Huntington's disease and with antipsychotic treatment in schizophrenia (72). There is also some preliminary evidence that children with dyspraxia may benefit from EFA supplementation (36).

Learning disabilities

ADHD frequently co-occurs with dyslexia, with the clinical overlap estimated at 30-50 per cent in both directions (73,74). The association with dyslexia appears to be stronger for attentional disorder without overt hyperactivity than it is for a predominantly hyperkinetic form of ADHD (28,74), and the shared features include specific problems in certain aspects of visual and cognitive function (73).

Fatty acid deficiency has been proposed as a contributory factor in dyslexia (23,35,37-39), and evidence is emerging that fatty acid supplementation may help to alleviate aspects of this disorder (36,75)

EVIDENCE FOR FATTY ACID DEFICIENCY IN ADHD

EFA deficiency in ADHD was first proposed by Colquhoun and Bunday (76), who set up a Hyperactive Children's Support Group (HCSG) in the UK. They conducted a survey of hyperactive children and found the usual excess of males, an association of with asthma, eczema and other allergic conditions, and evidence of zinc deficiency from hair analysis. Clinical signs consistent with EFA deficiency that were found in these children included: excessive thirst, frequent urination, dry skin and dry hair. They proposed that in ADHD there might be a problem in the conversion of EFAs to LC-PUFAs; no evidence was found of a dietary deficiency of the parent EFAs. It was suggested that this could help to explain the purportedly favourable response to the Feingold diet (77): this diet excludes naturally occurring salicylates, as found in some fruits, for example, and salicylates in turn inhibit the conversion of LC-PUFAs to prostaglandins. It could also explain the association with zinc deficiency, as zinc is an important cofactor in the conversion of EFAs to LC-PUFAs; zinc deficiency inhibits delta-6-desaturase (78). The HCSG recommended supplementation with LC-PUFAs, and their anecdotal evidence suggested that this might be helpful in at least some cases.

Blood biochemical studies subsequently provided supporting evidence for this hypothesis. Deficiencies of certain fatty acids (lower plasma levels of DGLA, AA and DHA) were found in 44 children with ADHD compared with 45 age- and sex-matched controls (79). In the same study, significantly more of 48 children with ADHD compared with 49 age- and sex-matched controls suffered from polydypsia and polyuria, as well as other health problems and language, reading and learning difficulties.

Studies carried out more recently at Purdue University provided further support for the proposal that fatty acid metabolism is abnormal in ADHD (80). This team found that, relative to 43 normal

controls, 53 boys with ADHD:

- were less likely to have been breastfed (breast milk contains the preformed LC-PUFAs such as AA and DHA, while most formula preparations do not)
- were more likely to suffer from allergies and other health problems (which are already known to be associated with EFA deficiency)
- showed clinical signs of EFA deficiency (such as polydypsia, polyuria, dry skin, and dry hair)
- showed reduced blood levels of certain LC-PUFAs (in plasma: reduced AA, EPA, DHA and lower total n-3 fatty acids; and in red cell membranes: reduced AA and adrenic acid but increased n-6 DPA, which typically accumulates under n-3 deficiency)
- showed no deficiency in the EFA precursors of these LC-PUFAs
- had an adequate dietary intake of the EFA precursors.

These results are consistent with the proposal that in at least a subset of ADHD children there may be some problem in the conversion of EFAs to LC-PUFAs. In this study, approximately 40 per cent of subjects with ADHD had an elevated frequency of clinical fatty acid deficiency signs, compared with only nine per cent of the control subjects.

Importantly, the same research group (81) has also shown that both clinical signs and blood biochemical measures of fatty acid deficiency were significantly associated with:

- the severity of reported behaviour problems (this applied to both n-3 and n-6 deficiency on biochemical measures)
- the incidence of learning and health problems (this applied to n-3 deficiency only).

Another group has also reported that, compared with 45 healthy age- and sex-matched children, the mean serum free fatty acid level in 48 children with ADHD was significantly lower (82). Furthermore, a statistically significant correlation was also found between zinc and free fatty acid levels in the ADHD group.

The above results support a relationship between n-3 fatty acid status and behaviour in children which parallels what is already known from animal studies. Moreover, this approach – investigating the associations between *specific* symptoms and behaviours and *specific* aspects of fatty acid status – seems a sensible one. It not only allows comparisons to be drawn with the now vast animal literature, but it also offers a realistic method of exploring the way in which fatty acid deficiencies may relate to such complex and multi-faceted disorders as ADHD.

CAN FATTY ACID SUPPLEMENTS HELP IN THE MANAGEMENT OF ADHD?

The consistent findings of both clinical signs of fatty acid deficiency and blood biochemical indices of fatty acid abnormalities in at least a subset of ADHD children indicate that supplementation with LC-PUFAs might be helpful in the management of this condition in at least some cases. The challenge is now to determine what proportion of children with an ADHD diagnosis might benefit from such supplementation, and how they may best be identified. To date, only a few preliminary pilot studies have been published.

Two early double-blind placebo-controlled trials of GLA supplementation gave equivocal results in ADHD subjects who had not been selected as having low levels of n-6 fatty acids (83,84). In the second of these studies, with 18 subjects, modest benefits over placebo were reported for GLA supplementation, although this was less effective than D-amphetamine (84). In addition, the level of serum triglyceride GLA was found to correlate inversely with Conners' scale scores (85). This finding of only a modest benefit from GLA is perhaps unsurprising, for a number of reasons. Evidence gathered since then suggests that n-3 rather than n-6 fatty acid deficiency may be of more

relevance in ADHD. Another fundamental issue is that the study design and treatment duration (subjects in the second study were randomly allocated to GLA, D-amphetamine or placebo for one month each), cannot be considered appropriate for the evaluation of fatty acid treatment. Unlike D-amphetamine, fatty acids cannot be expected to act rapidly to change symptoms or behaviour. Rather, recent evidence has shown that LC-PUFA levels in the brain may take up to three *months* to recover from a chronic deficiency state (86,87), and this must therefore be regarded as an essential consideration in the design of future treatment studies.

More recently, the Purdue group gave a preliminary report on the results of a randomized, double-blind treatment trial in ADHD children with clinical signs of fatty acid deficiency (88). They found that supplementation with a combination of DHA, EPA, AA and DGLA (weighted in favour of the n-3 fatty acids) was successful in changing the blood fatty acid profile of ADHD children, and that this was associated with reductions in ADHD symptoms. However, at the same meeting, preliminary results from another randomized double-blind treatment trial showed no benefits from supplementation with pure DHA (89). Different treatments, procedures and measures were used in these two studies, making them difficult to compare. One possibility is that DHA alone is indeed ineffective, and that other fatty acids - particularly EPA - may account for the benefits found in the Purdue study. However, another very important factor could be the differences in subject selection. While the Purdue study involved selecting children on the basis of prior indications of fatty acid deficiency, in the other study no such pre-treatment indices were used; instead, extremely strict exclusion criteria were applied, ruling out any comorbidity and ensuring that the sample consisted of children with 'pure' ADHD diagnoses. In any case, a proper evaluation of either trial must await full publication.

At the time of writing a full report of the Purdue study is in preparation (90), and another study by the authors of this paper is approaching completion.

CONCLUSIONS

We would suggest that, based on the above evidence, there is a very strong case for further research into the rôle of fatty acids in ADHD and related disorders. However, it seems crucial that such investigations should be hypothesis-driven, and at this stage some general recommendations can be made in the light of existing findings.

First, there is a clear need to identify more precisely the clinical features that best characterize those children who do show fatty acid deficiencies on biochemical testing. Given the existing evidence from blood biochemical studies, and the acknowledged clinical heterogeneity of children who meet current diagnostic criteria for ADHD, it seems unlikely that fatty acid deficiencies will seriously affect more than a subset of these children. Blood biochemical analyses of fatty acid status should therefore be incorporated where possible into studies carefully designed to explore the issue of heterogeneity. A primary aim should be to establish what relationships there may be between reliable measures of fatty acid deficiency (including the precise nature of such deficiency patterns) and particular clinical symptoms and aspects of behaviour. To give just one example, there is evidence that DHA supplementation can protect against stress-induced aggression in normal subjects (91), suggesting that it may well be worthwhile to investigate levels of this particular fatty acid in relation to aggressive tendencies and stress-susceptibility within ADHD.

Second, particular attention should be paid to comorbidity issues. The available evidence suggests that fatty acid deficiency may prove to be an important factor in many disorders that often co-occur with ADHD, notably mood disorders, dyspraxia and dyslexia. Specifically, we would argue that relationships between biochemical measures of fatty acid metabolism, symptoms and behaviour require further study, *irrespective* of the clinical diagnosis that may be considered to be primary. There is often a tendency to seek 'pure' cases for inclusion in research studies, but in determining what rôle fatty acids (or any other low-level, biochemical factors) might play in complex clinical disorders, this approach may have serious limitations. Again, it should be possible

to generate realistic and testable hypotheses based on existing evidence. For example, the current evidence implicating n-3 deficiency in depression invites an examination of this issue in ADHD subjects with and without significant mood disorder.

Finally, treatment issues require careful and systematic investigation. Anecdotal evidence of benefits has already led to a situation in which many parents, teachers and clinicians are prepared to try or to recommend dietary supplementation with fatty acids in the management of ADHD. However, until further data are available, no recommendations can be made concerning the efficacy of fatty acid supplementation as a treatment for this condition. Furthermore, while it is true that LC-PUFA supplements have few, if any, contra-indications (and a number of established health benefits), medical advice should always be sought before commencing any dietary supplementation programme. There is now an obvious need for more randomized, double-blind, placebo-controlled trials of supplementation with LC-PUFAs, but these need to be designed with several caveats in mind. In particular, there need to be clear hypotheses, subject numbers must be sufficient to test these, and both the choice of treatments and the duration (ideally, a minimum of several months) are likely to be crucial. In addition, treatment can only reasonably be expected to be of significant benefit in cases where there is a pre-existing fatty acid deficiency. Thus it seems probable that concerted efforts to delineate such a subset of children will prove more fruitful than an exclusive focus on the clinical diagnosis of ADHD.

REFERENCES

1. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Geneva: World Health Organization, 1992.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). Washington DC: American Psychiatric Association, 1994.
3. Holman RT. The slow discovery of the importance of T3 essential fatty acids in human health. J Nutr 1998; 128: 427S-433S.
4. Nunez EA. Fatty acids and cell signalling. Prostaglandins Leukotr Essent Fatty Acids 1993; 48: 1-122.
5. Delion S, Chalon S, Herault J, Guilloteau D, Besnard J-C, Durand G. Chronic dietary α-linolenic acid deficiency alters dopaminergic and serotonergic neurotransmission in rats. J Nutr 1994; 124: 2466-2476.
6. Nishikawa M, Kimura S, Akaitke N. Facilitatory effect of docosahexaenoic acid on N-methyl-D-aspartate response in pyramidal neurons of rat cerebral cortex. J Physiol 1994; 475: 83-93.
7. Yoshida S, Sato A, Okuyama H. Pathophysiological effects of dietary essential fatty acid balance on neural systems. Jpn J Pharmacol 1998; 77: 11-22.
8. Johnston M, Carey F, McMillan RM. Alternative pathways of arachidonate metabolism: prostaglandins, thromboxane and leukotrienes. In: Campbell PN, Marshall RD, eds. Essays in Biochemistry. London: Academic Press, 1983: 40-141.
9. Crawford MA. Essential fatty acids and neurodevelopmental disorder. In: Bazan NG, ed. Neurobiology of Essential Fatty Acids. New York: Plenum Press, 1992: 307-314.
10. Yamamoto N, Saitoh M, Moriuchi A, Nomura, M Okuyama H. Effect of dietary alpha linolenate/linoleate balance on brain lipid composition and learning ability in rats. J Lipid Res 1987; 28: 144-151.
11. Neuringer M, Anderson GJ, Connor WE. The essentiality of n-3 fatty acids for the development and function of the retina and brain. Annu Rev Nutr 1988; 8: 517-541.
12. Bourre J-M, Marianne F, Youyou A, et al. The effects of dietary alpha-linolenic acid on the composition of nerve membranes, enzymatic activity, amplitude of electrophysiological parameters, resistance to poisons and performance of learning tasks in rats. J Nutr 1989; 119: 1880-1891.
13. Neuringer M, Reisbeck S, Janowsky J. The role of n-3 fatty acids in visual and cognitive development: Current evidence and methods of assessment. J Pediatr 1994; 125: S39-47.
14. Neuringer MD, Connor WE, Lin DS, Barstad L, Luck S. Biochemical and functional effects of prenatal and postnatal ω-3 fatty acid deficiency on retina and brain in rhesus monkeys. Proc Natl Acad Sci USA 1986; 83: 4021-4025.
15. Dobbing J, ed. Developing Brain and Behaviour: The Role of Lipids in Infant Formula. London: Academic Press, 1997.
16. Makrides M, Newmann M, Simmer K, Pater J, Gibson R. Are long-chain polyunsaturated fatty acids essential nutrients in infancy? Lancet 1995; 345: 1463-1468.
17. Brenner RR. Nutritional and hormonal factors influencing desaturation of essential fatty acids. Prog Lipid Res 1981; 20: 41-47.
18. Manku MS, Horrobin DF, Morse NL, Wright S, Burton JL. Essential fatty acids in the plasma phospholipids of patients with atopic eczema. Br J Dermatol 1984; 110, 643-648.

19. Wright S, Bolton C. Breast milk fatty acids in children with atopic eczema. Br J Nutr 1989; 62: 693-697.
20. Ewald U, Gustafsson IB, Tuvemo T, Vessby B. Fatty acid composition of serum lipids in diabetes. Ups J Med Sci 1982; 87: 111-117.
21. Arisaka M, Arisaka O, Fukuda Y, Yamashiro Y. Prostaglandin metabolism in children with diabetes mellitus. I. Plasma prostaglandin E2, F2a, TXB2 and serum fatty acid levels. J Pediatr Gastroenterol Nutr 1986; 5: 878-882.
22. Horrobin DF. The roles of essential fatty acids in the development of diabetic neuropathy and other complications of diabetes mellitus. Prostaglandins Leukotr Essent Fatty Acids 1988; 31: 181-197.
23. Horrobin DF, Glen AIM, Hudson CJ. Possible relevance of phospholipid abnormalities and genetic interactions in psychiatric disorders: the relationship between dyslexia and schizophrenia. Med Hypotheses 1995; 45: 605-613.
24. Witt MR, Nielsen M. Characterisation of the influence of unsaturated free fatty acids on brain GABA/benzodiazepine receptor binding in vitro. J Neurochem 1994; 62: 1432-1439.
25. Horrobin DF. Schizophrenia as a membrane lipid disorder which is expressed throughout the body. Prostaglandins Leukotr Essent Fatty Acids 1996; 55: 3-7.
26. Zimmer L, Hembert S, Durand G, et al. Chronic n-3 polyunsaturated fatty acid diet-deficiency acts on dopamine metabolism in the rat frontal cortex: a microdialysis study. Neurosci Lett 1998; 240, 177-181.
27. Francàs H, Monier C, Bourre JM. Effects of dietary alpha-linolenic acid deficiency on neuromuscular and cognitive functions in mice. Life Sci 1995; 57: 1935-1947.
28. Hynd GW, Lorys AR, Semrud-Clikeman M, Nieves N, Huettner MIS, Lahey BB. Attention-deficit disorder without hyperactivity: a distinct behavioural and neurocognitive syndrome. J Child Neurol 1991; 6(suppl): 35-41.
29. Trites RL, Dugas F, Lynch G, Ferguson B. Incidence of hyperactivity. J Pediatr Psychol 1979; 4: 179-188.
30. Szatmari P, Offord DR, Boyle MH. Ontario child health study: prevalence of attention deficit disorder with hyperactivity. J Child Psychol Psychiatry 1989; 30: 219-230.
31. Ross DM, Ross SA. Hyperactivity: Current Issues, Research, and Theory. 2nd ed. New York: Wiley, 1982.
32. Pudelkewicz C, Seufert J, Holman RT. Requirements of the female rat for linoleic and linolenic acids. J Nutr 1968; 64: 138-147.
33. Huang YS, Horrobin DF, Watanabe Y, Bartlett ME, Simmons VA. Effects of dietary linoleic acid on growth and liver phospholipid fatty acid composition in intact and gonadectomized rats. Biochem Arch 1990; 6: 47-54.
34. Horrobin DF, Glen AIM, Vaddadi K. The membrane hypothesis of schizophrenia. Schizophr Res 1994; 13: 195-207.
35. Stordy BJ. Benefit of docosahexaenoic acid supplements to dark adaptation in dyslexia. Lancet 1995; 346: 385.
36. Stordy BJ. Dark adaptation, motor skills, docosahexaenoic acid, and dyslexia. Am J Clin Nutr 2000; 71(suppl 1): 323S-326S.
37. Richardson AJ, Cox IJ, Sargentoni J, Puri BK. Abnormal cerebral phospholipid metabolism in dyslexia indicated by phosphorus-31 magnetic resonance spectroscopy. NMR Biomed 1997; 10: 309-314.
38. Richardson AJ, Easton T, Corrie AC, Clisby C, Stordy BJ. Is developmental dyslexia a fatty acid deficiency syndrome? (abstract) Proc Nutr Soc 1998.
39. Richardson AJ, Easton T, McDaid AM, et al. Essential fatty acids in dyslexia: theory, evidence and clinical trials. In: Peet M, Glen I, Horrobin DF, eds. Phospholipid Spectrum Disorder in Psychiatry. Carnforth: Marius Press, 1999: 225-241.
40. Puri BK, Richardson AJ. Sustained remission of positive and negative symptoms of schizophrenia following treatment with eicosapentaenoic acid. Arch Gen Psychiatry 1998; 55: 188-189.
41. Firestone P, Lewy F, Douglas VI. Hyperactivity and physical anomalies. Can Psychiatr Assoc J 1976; 21: 23-26.
42. Lerer RJ. Do hyperactive children tend to have abnormal palmar creases? Report of a suggestive association. Clin Pediatr 1977; 16: 645-647.
43. Quinn PO, Rapoport JL. Minor physical anomalies and neurological status in hyperactive boys. Pediatrics 1974; 53: 742-747.
44. Kaufmann WE, Worley PF, Pegg J, Bremer M, Isakson P. COX-2, a synaptically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. Proc Natl Acad Sci USA 1996; 93: 2317-2321.
45. Smalheiser NR, Dissanayake S, Kapil A. Rapid regulation of neurite outgrowth and retraction by phospholipase A_2-derived arachidonic acid and its metabolites. Brain Res 1996; 721: 39-48.
46. Hughes DA, Southon S, Pinder AC. n-3 Polyunsaturated fatty acids modulate the expression of functionally associated molecules on human monocytes in vitro. J Nutr 1996; 126: 603-610.
47. Kaplan BJ, McNichol J, Conte RA, Moghadam HK. Sleep disturbance in preschool-aged hyperactive nonhyperactive children. Pediatrics 1987; 80: 839-844.
48. Trommer BL, Hoeppner JB, Rosenberg RS, Armstrong KJ, Rothstein JA. Sleep disturbances in children with attention deficit disorder. Ann Neurol 1988; 24: 325.
49. Fagioli I, Baroncini P, Ricour C, Salzarulo P. Decrease of slow-wave sleep in children with prolonged absence of essential lipids intake. Sleep 1989; 12: 495-499.
50. Yehuda S, Rabinovitz S, Mostofsky DI. Essential fatty acids and sleep: mini-review and hypothesis. Med Hypotheses 1998; 50: 139-145.
51. Hartsough CS, Lambert NM. Medical factors in hyperactive and normal children: prenatal, developmental, and health history findings. Am J Orthopsychiatry 1985; 55: 190-210.
52. Szatmari P, Offord DR, Boyle MH. Correlates, associated impairments, and patterns of service utilization of

children with attention deficit disorders: findings from the Ontario child health study. J Child Psychol Psychiatry 1989; 30: 205-217.
53. Horrobin DF. Post-viral fatigue syndrome, viral infections in atopic eczema, and essential fatty acids. Med Hypotheses 1990; 32: 211-217.
54. Barkley RA. Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment. 2nd ed. New York: Guildford Press, 1998.
55. Horrobin DF. Essential fatty acids, immunity and viral infections. J Nutr Med 1990; 1: 145-151.
56. Alexander JW. Immunonutrition: the role of omega-3 fatty acids. Nutr 1998; 14: 627-633.
57. Miles EA, Calder PC. Modulation of immune function by dietary fatty acids. Proc Nutr Soc 1998; 57: 277-292.
58. Holman RT. The slow discovery of the importance of T3 essential fatty acids in human health. J. Nutr 1998; 128: 427S-433S.
59. Biederman J, Munir K, Knee D, et al. High rate of affective disorders in probands with attention deficit disorders and in their relatives: a controlled family study. Am J Psychiatry 1987; 144: 330-333.
60. Barkley RA, Fischer M, Edelbrock CS, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. Am Acad Child Adolesc Psychiatry 1990; 29: 546-557.
61. Barkley RA, Fischer M, Fletcher K, Smallish L. Young adult outcome of hyperactive children diagnosed by research criteria. NIH Consensus Meeting on ADHD. National Institutes of Health: Bethesda, 1998.
62. Biederman J, Faraone S, Milberger S, et al. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. Arch Gen Psychiatry 1996; 53: 437-446.
63. Hibbeln JR and Salem N. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. Am J Clin Nutr 1995; 62: 1-9.
64. Hibbeln JR. Fish consumption and major depression. Lancet 1998; 351: 1213.
65. Maes M, Smith RS. Fatty acids, cytokines, and major depression. Biol Psychiatry 1998; 43: 313-314.
66. Maes M, Smith R, Christophe A, Cosyns P, Desnyder R, Meltzer H. Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20:4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids J Affect Disord 1996; 38: 35-46.
67. Peet M, Murphy B, Shay J, Horrobin D. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. Biol Psychiatry 1998; 43: 315-319.
68. Stoll AL, Severus E, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. Arch Gen Psychiatry 1999; 56: 407-412.
69. Denckla MB, Rudel RG. Anomalies of motor development in hyperactive boys. Ann Neurol 1978; 3: 231-233.
70. Denckla MB, Rudel RG, Chapman C, Krieger J. Motor proficiency in dyslexic children with and without attentional disorders. Arch Neurol 1985; 42: 228-231.
71. Nilsson A, Horrobin DF, Rosengren A, Waller L, Adlerberth A, Wilhelmson L. Essential fatty acids and abnormal involuntary movements in the general male population: a study of men born in 1933. Prostaglandins Leukotr Essent Fatty Acids 1996; 55: 83-87.
72. Vaddadi K. Dyskinesias and their treatment with essential fatty acids: a review. Prostaglandins Leukotr Essent Fatty Acids 1996; 55: 89-94.
73. Conners CK. Dyslexia and the neurophysiology of attention. In: Pavlidis GTh, ed. Perspectives on Dyslexia, Volume 1. Chichester: Wiley, 1990: 163-195.
74. Dykman RA, Ackerman PT. Attention deficit disorder and specific reading disability: separate but often overlapping disorders. J Learn Disabil 1991; 24: 96-103.
75. Baker SM. A biochemical approach to the problem of dyslexia. J Learn Disabil 1985; 18: 581-584.
76. Colquhoun I, Bunday S. A lack of essential fatty acids as a possible cause of hyperactivity in children. Med Hypotheses 1981; 7: 673-679.
77. Feingold BF. Why Your Child is Hyperactive. New York: Random House, 1975.
78. Huang YS, Cunnane SC, Horrobin DF, et al. Most biological effects of zinc deficiency corrected by gamma-linolenic acid but not by linoleic acid. Atherosclerosis 1982; 41: 193-207.
79. Mitchell EA, Aman MG, Turbott SH, Manku M. Clinical characteristics and serum essential fatty acid levels in hyperactive children. Clin Pediatr 1987; 26: 406-411.
80. Stevens LJ, Zentall SS, Deck JL, et al. Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder Am J Clin Nutr 1995; 62: 761-768.
81. Stevens LJ, Zentall SS, Abate ML, Kuczeck T, Burgess JR. Omega-3 fatty acids in boys with behavior, learning and health problems. Physiol Behav 1996; 59: 915-920.
82. Bekaroglu M, Aslan Y, Gedik Y, et al. Relationships between serum free fatty acids and zinc, and attention deficit hyperactivity disorder: a research note. J Child Psychol Psychiatry 1996; 37: 225-227.
83. Aman MG, Mitchell EA, Turbott SH. The effects of essential fatty acid supplementation by Efamol in hyperactive children. J Abnorm Child Psychol 1987; 15: 75-90.
84. Arnold LE, Kleykamp D, Votolato NA, Taylor WA, Kontras SB, Tobin K. Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. Biol Psychiatry 1989; 25: 222-228.
85. Arnold LE, Kleykamp D, Votolato NA, Gibson RA, Horrocks L. Potential link between dietary intake of fatty acids and behavior: pilot exploration of serum lipids in ADHD. J Child Adolesc Psychopharmacol 1994; 4: 171-180.

86. Bourre J-M, Bonneil M, Clement M, et al. Function of dietary polyunsaturated fatty acids in the nervous sytem. Prostaglandins Leukotr Essent Fatty Acids 1993; 48: 5-15.
87. Bourre J-M, Durand G, Pascal G, Youyou A. Brain cell and tissue recovery in rats made deficient in n-3 fatty acids by alteration of dietary fat. J Nutr 1988; 119: 15-22.
88. Burgess JR. Attention deficit hyperactivity disorder: observational and interventional studies. NIH workshop on omega-3 essential fatty acids and psychiatric disorders. National Institutes of Health: Bethesda, 1998, Sept. 2-3.
89. Voight R. Attention deficit hyperactivity disorder: observational and interventional studies. NIH workshop on omega-3 essential fatty acids and psychiatric disorders. National Institutes of Health: Bethesda, 1998, Sept. 2-3.
90. Burgess JR, Stevens L, Zhang W, Peck L. Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. Am J Clin Nutr 2000; 71: 327-330.
91. Hamazaki T, Sawazaki S, Itomura M, et al. The effect of docosahexaenoic acid on aggression in young adults. A placebo-controlled double-blind study. J Clin Invest 1996; 97: 1129-1133.

Fig. 1 The elongation and desaturation pathways for the synthesis of n-6 and n-3 fatty acids

n-6 Fatty Acids			**n-3 Fatty Acids**	
Linoleic (LA)	18:2		Alpha-linolenic (ALA)	18:3
↓		*Delta 6-desaturase*	↓	
Gamma-linolenic (GLA)	18:3		Octadecatetraenoic	18:4
↓		*Elongase*	↓	
Dihommogamma-linolenic (DGLA)	20:3		Eicosatetraenoic	20:4
↓		*Delta 5-desaturase*	↓	
Arachidonic (AA)	20:4		**Eicosapentaenoic (EPA)**	20:5
↓		*Elongase*	↓	
Adrenic	22:4		Docosapentaenoic (DPA)	22:5
↓		*Elongase*	↓	
Tetracosatetraenoic	24:4		Tetracosapentaenoic	24:5
↓		*Delta 6-desaturase*	↓	
Tetracosapentaenoic	24:5		Tetrahexaenoic	24:6
↓		*Beta-oxidation*	↓	
Docosapentaenoic (DPA)	22:5		**Docosahexaenoic (DHA)**	22:6