

Fatty acid metabolism in health and disease: the role of Δ -6-desaturase¹

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ABSTRACT Linoleic acid is the main dietary essential fatty acid (EFA). To be fully utilized by the body, it must be metabolized to a range of other substances. The first step in this pathway is Δ -6-desaturation to γ -linolenic acid (GLA). This step is slow and rate-limiting, particularly in humans. If Δ -6-desaturation is impaired for any reason, the supply of further metabolites may be inadequate for normal function. If the consumption of further metabolites is excessive, then a normal rate of Δ -6-desaturation may be inadequate. In these circumstances the direct supply of GLA or further metabolites may be of value. This concept is illustrated by atopic eczema and diabetes, which may represent inherited and acquired examples of inadequate Δ -6-desaturation. *Am J Clin Nutr* 1993;57(suppl):732S-7S.

KEY WORDS Essential fatty acids, linoleic acid, Δ -6-desaturation, eczema, diabetes mellitus

Introduction

The two main dietary essential fatty acids (EFAs) are linoleic acid (LA) of the n-6 series and α -linolenic acid (ALA) of the n-3 series. They are metabolized within the body by the sequence of reactions shown in **Figure 1**. In turn, several of the fatty acids shown in Figure 1, notably dihomo- γ -linolenic acid (DGLA), arachidonic acid, and eicosapentaenoic acid (EPA) can give rise to a wide range of short-lived metabolites known collectively as the eicosanoids. The EFAs and the eicosanoids play important roles in both the structure and function of every cell in the body. This paper is primarily concerned with the n-6 EFAs, although because the n-3 EFAs are metabolized by the same enzyme sequence, much of what is said is relevant to the n-3 pathway also.

LA itself carries out few of the functions of an EFA. By itself, it maintains the water impermeability of the skin, but for its other effects it requires metabolism, first to γ -linolenic acid (GLA) by Δ -6-desaturation, and then on to other substances. Perhaps the most convincing evidence that metabolism is necessary are 1) the increasing potency of each substance as an EFA in both biological and biochemical assays as one moves down the chain from linoleic to arachidonic acid (1, 2) and 2) the EFA requirements of cats (3). Cats have little or no Δ -6-desaturase activity, and LA has correspondingly little EFA activity; GLA, which bypasses the Δ -6-desaturation step, is an effective EFA in the cat (3).

Thus LA (and also ALA) might be regarded in a sense as analogues to provitamins. To exert their full range of biological

activity, they must be metabolized to other substances. This means that Δ -6-desaturation plays a crucial role in ensuring the normal function of animals.

There has recently been much concern about Δ -6-desaturation in relation to infant nutrition. Human milk is unusual because it contains a range of fatty acids, such as GLA, DGLA, arachidonic acid, EPA, and docosahexaenoic acid, which have all undergone 6-desaturation (4, 5). In contrast, conventional infant-formula milks contain only LA and ALA, so the infant must perform its own desaturation reactions to produce the EFA metabolites required for normal function of all organs, including the immune system and the brain. There is concern that the human infant's desaturating systems may be too immature to cope (6, 7), as indicated by the finding that the blood concentrations of LA and ALA metabolites are higher in breast-fed than in bottle-fed infants (8). This is an emerging issue of major practical importance, as indicated by the fact that 8-y-old children who were fed expressed breast milk as premature infants have intelligence quotients \approx 8 points higher than similar children who were fed formula as infants (9). This is a very large difference, and although the mechanism is as yet unknown, the high concentrations in human milk of metabolites of LA and ALA are strong candidates in view of their importance in the brain (9).

The possibility that inadequate Δ -6-desaturation may play a role in some human diseases, as opposed to normal development, will now be discussed in relation to two specific examples, atopic eczema and diabetes mellitus.

Atopic eczema

Atopic eczema is an inherited form of dermatitis that almost always develops initially during the first year of life. It remits and relapses throughout life, often showing considerable improvement around the time of puberty. Patients with atopic eczema are more susceptible than normal to viral infections and to allergic reactions of various types. They have abnormal immune function, with high concentrations of immunoglobulin E (IgE) and an elevated ratio of T-helper to T-suppressor lymphocytes.

Knowledge of the relationship of EFAs to dermatitis is as old as knowledge of the EFAs themselves. Dermatitis is consistently

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the first sign of EFA deficiency in both animals and humans, and one of the technicians employed by the Burrs, who discovered EFAs, reported that his hand dermatitis improved on increasing his EFA intake (10). Hansen, a pediatrician friend of the Burrs, thought that the dermatitis in EFA-deficient rats resembled the atopic eczema in his children and initiated a long series of studies on EFAs and dermatitis (see refs 11–13). He reported that the blood concentrations of EFAs were low in atopic eczema and that the condition responded to very high doses of LA (20–50 g/d). Lower LA doses were ineffective, ruling out the possibility that atopic eczema was a simple EFA-deficiency disease.

In retrospect, one of Hansen's most important studies was one in which, using crude methodology, he found that LA concentrations in blood in eczema patients treated with LA were normal, whereas arachidonic acid concentrations were well below normal (12). At that time it was not known that LA was converted to arachidonic acid within the body, but with hindsight this result may be interpreted as indicating that the conversion of LA to arachidonic acid was impaired.

For about 20 y, until 1955, the use of very high doses of LA was one of the standard approaches to treating atopic eczema. However, the treatment was unpalatable to most patients and when topical steroids were introduced with their dramatic symptomatic relief of eczema, the nutritional approach fell into disuse. It was revived again 25 y later, partly as a result of new work on EFAs and the skin and partly as a consequence of the recognition that the steroids did nothing to change the course of the disease and had important adverse effects.

Adult patients with atopic eczema were compared with normal individuals with regard to the fatty acid composition of plasma phospholipids (14, 15). Linoleic acid concentrations were slightly above normal, indicating adequate intake and absorption of the main dietary EFAs. In contrast, concentrations of GLA, DGLA, and arachidonic acid were below normal. This suggested either that Δ -6-desaturase activity was somewhat reduced in atopic eczema, or that consumption of the metabolites was excessive and could not be compensated by the rate-limiting enzyme. Bypassing the Δ -6-desaturase by giving GLA in the form of evening primrose oil (Epogam; Scotia Pharmaceuticals, Guildford, UK) led to a partial normalization of phospholipid composition and an increase in the formation of prostaglandin E_1 (14).

Several other observers have now confirmed the abnormal EFA pattern in atopic eczema, a pattern demonstrated by modern gas chromatography, which is nevertheless consistent with Hansen's 1937 paper (12). The same pattern of elevated or upper-range-of-normal LA concentrations with reduced concentrations of LA metabolites has been found in children with atopic eczema (18), in cord blood and cord-blood lymphocytes of babies at risk of atopic eczema because of genetic history (18, 19), in triglycerides of adipose tissue (17) and of breast milk in people with atopic eczema (18), and in red cells of eczema patients (20). The elevation of LA in umbilical-cord blood was positively correlated with the elevation of IgE concentrations in the same samples.

The detection of an apparent abnormality of EFA metabolism in umbilical-cord blood and lymphocytes before the dermatitis has developed clearly shows that the EFA abnormality precedes the skin condition and is therefore a candidate for its cause. One test of this is to administer GLA in placebo-controlled studies. Many of these have now been set up, and in almost all, active treatment with GLA as evening primrose oil has been more

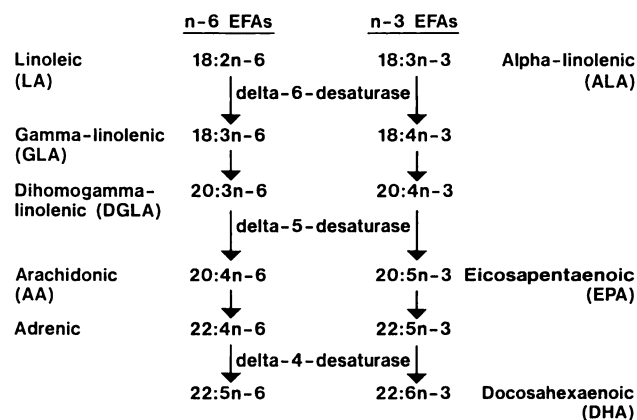


FIG 1. An outline of essential fatty acid (EFA) metabolism.

effective than placebo in producing clinical improvement (21–30). Paraffin and olive oil have been used for the placebos. In a recent study, Gibson and Heddle used safflower oil, rich in linoleic acid, as a placebo (31). The safflower oil group deteriorated while the GLA group improved during treatment. It seems unlikely that the linoleic acid in evening primrose oil is beneficial since it provides only 2 g/d, 10–20% of the normal daily intake.

Itch is the symptom that seems to respond most to GLA (25). There is also a significant reduction in the need for potentially harmful steroids (22) and a significant improvement in the rough skin that is a characteristic feature of atopic eczema (27, 28).

Hansen—with his observations in the 1930s and his suggestion that atopic eczema might be a disorder of EFA metabolism—has therefore been vindicated: the suggestion and observations had been forgotten for 25–30 y. GLA as Epogam is now an officially licensed treatment for atopic eczema in the UK, Ireland, Denmark, Germany, Italy, South Africa, and Australia.

Diabetes mellitus

In diabetes the disorder of EFA metabolism is acquired and is superimposed on all the complex abnormalities of carbohydrate and lipid metabolism characteristic of the disease. It was first reported in the 1950s that diabetic animals required much more linoleic acid than did normal animals (32). The possible reason for this was discovered a decade later, when Brenner's group in Argentina discovered that in diabetic animals the activity of the Δ -6-desaturase enzyme was greatly impaired (33). Because linoleic acid exerts most of its biological effects by being converted to GLA and beyond, this meant that in diabetes the proportion of dietary LA that was biologically effective was reduced. The need for an increased intake was therefore not surprising.

Brenner's observations have been repeatedly confirmed in animals by his own and many other different laboratories (34–38). In humans direct evidence of impaired conversion of LA to GLA is hard to come by for ethical reasons. However, there is much indirect evidence. Linoleic acid concentrations are almost always normal or slightly above normal in diabetic patients, whereas the concentrations of linoleic acid metabolites are consistently below normal (39–42). When diabetics are treated with continuous subcutaneous insulin therapy, the concentrations of its major metabolites rise significantly (43).

Perhaps the main problem in the management of diabetes is the development of long-term damage to the retina, the kidneys, the cardiovascular system, and the peripheral nerves. Although there are many hypotheses, none has found universal acceptance and treatment is generally unsatisfactory. Good control of blood glucose may be beneficial, but many well-controlled diabetics develop severe complications whereas some poorly controlled diabetics do not.

It is possible that the increased requirement for EFAs is an important factor in the development of diabetic complications. This was first tested by Patterson (44) and by Patterson et al (45), who showed that diabetic cataract in rats could be completely prevented by raising the LA content of the diet (44, 45). His work has been substantially confirmed by later investigators (46). In 1959 Kinsell et al reported in uncontrolled studies that increased LA could reverse the development of diabetic retinopathy (47). This was later confirmed in controlled studies by King et al (48) in London, Houtsmuller et al (49) in Rotterdam, and Howard-Williams et al (50) in Oxford. Large amounts of LA in the range of 30–50 g are required for the effect. Unfortunately, many patients find the diets unpalatable, and compliance is poor (50). Possibly for this reason, and possibly also because the approach has not attracted any commercial sponsorship, high-LA diets, despite their obvious success, are not recommended to many patients.

An alternative approach, which might be successful in much lower amounts, would be to supplement the diet with GLA directly. Because EFAs and their metabolites are exceptionally important in both the structure and function of nerves (51, 52), it seemed to me possible that diabetic nerve damage (neuropathy) might be particularly responsive to this approach. The neuropathy is an important cause of problems in diabetics, being particularly responsible for clinically detectable sensory impairment in about half of all diabetics. Neurophysiologically detectable damage to nerve function occurs in more than 90% of diabetics (53). The neuropathy leads to many further complications including skin ulceration, limb amputation, impotence, and bladder, gastrointestinal, and cardiovascular disturbances.

A pilot study was set up in Glasgow in which 22 diabetics with neuropathy were randomly assigned to receive placebo or 320 mg of GLA/d as evening primrose oil (Efabetic; Scotia Pharmaceuticals). Treatment was continued for 6 mo and an extensive battery of double-blind clinical and neurophysiological tests was performed. At the end of the trial, values of all tested variables had improved in the GLA group but had remained more or less unchanged or had deteriorated in the placebo group (54).


A range of animal experiments provided similar results. Julu (55, 56) found that GLA could both prevent and reverse the neuropathy that develops in sural and sciatic nerves in diabetic animals. There was no effect on blood glucose and so the effect could not be attributed to improved diabetic control. Cameron et al (57) and Tomlinson et al (58, 59) independently obtained similar results. Again, improvement could not be attributed to improved control or to changes in the polyol pathway of glucose metabolism (58, 59). LA did not have any effect (57).

The animal studies and the pilot human study encouraged us to set up a major, seven-center clinical study. As before, treatments were randomized and double-blind but they lasted 12 mo rather than 6 mo. One hundred and thirteen patients were recruited to the study. The effects were similar to those of the pilot

study. All the clinical and neurophysiological features of the neuropathy improved during GLA treatment and deteriorated during the year on placebo. For 13 of the 16 variables the difference between active and placebo treatment was statistically significant (60).

Thus there can now be no doubt on the basis of animal and human studies performed in many centers that the neuropathy of diabetes can be both prevented and reversed by the administration of GLA. In view of the results achieved by high doses of LA on the retinopathy and other diabetic complications, there is a reasonable possibility that the retinopathy may also respond to GLA. A pilot placebo-controlled study has indicated that this may indeed be the case (61).

Conclusions

In two situations it has now been reasonably well-established that the rate-limiting nature of Δ -6-desaturation contributes to the development of diseases, namely atopic eczema and diabetic neuropathy. Bypassing the rate-limiting step by using GLA may have further desirable effects, particularly in the cardiovascular and anti-inflammatory areas (62–64). Extensive ongoing animal and clinical studies should allow definitive descriptions of the roles of Δ -6-desaturation and of GLA to emerge in the next 5 y. 

References

1. Thomasson HJ. Essential fatty acids. *Nature* 1954;173:452.
2. Hassam AG, Rivers JPW, Crawford MA. Metabolism of gamma-linolenic acid in essential fatty acid-deficient rats. *J Nutr* 1977;107:519–24.
3. Frankel TL, Rivers JPW. The nutritional and metabolic impact of gamma-linolenic acid on cats deprived of animal lipid. *Br J Nutr* 1978;39:227–31.
4. Gibson RA, Kneebone GM. Fatty acid composition of human colostrum and mature breast milk. *Am J Clin Nutr* 1981;34:252–7.
5. Harzer G, Haug M, Dieterich I, Gentner PR. Changing patterns of human milk lipids in the course of lactation and during the day. *Am J Clin Nutr* 1983;37:612–21.
6. Crawford MA, Doyle W, Drury P, Lennon A, Costeloe K, Leighfield M. n-6 and n-3 fatty acids during early human development. *J Intern Med* 1989;225:159–69.
7. Clandinin MT, Chappell JE, van Aerde EE. Requirements of newborn infants for long chain polyunsaturated fatty acids. *Acta Paediatr Scand* 1989;351:63–71.
8. De-Lucchi C, Pita ML, Faus MJ, Periago JL, Gil A. Influences of diet and postnatal age on the lipid composition of red blood cell membrane in newborn infants. *Ann Nutr Metab* 1988;32:231–9.
9. Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born pre-term. *Lancet* 1992;339:261–4.
10. Holman RT. George O Burr and the discovery of essential fatty acids. *J Nutr* 1988;118:535–40.
11. Hansen AE. Serum lipids in eczema and other pathological conditions. *Am J Dis Child* 1937;53:933–46.
12. Brown WR, Hansen AE. Arachidonic acid and linoleic acid of serum in normal and eczematous human subjects. *Proc Soc Exp Biol Med* 1937;30:113–6.
13. Hansen AE, Knott EM, Wiese HF. Eczema and essential fatty acids. *Am J Dis Child* 1947;73:1–18.
14. Manku MS, Horrobin DF, Morse N, et al. Reduced levels of prostanoid precursors in the blood of atopic patients: defective delta-

- 6-desaturase function as a biochemical basis for atopy. *Prostaglandins Leukot Med* 1982;9:615-28.
15. Manku MS, Horrobin DF, Morse NL et al. Essential fatty acids in the plasma phospholipids of patients with atopic eczema. *Br J Dermatol* 1984;110:643-8.
 16. Strannegard I-L, Svennerholm L, Strannegard O. Essential fatty acids in serum lecithin of children with atopic dermatitis and in umbilical cord serum of infants with high or low IgE levels. *Int Arch Allergy Appl Immunol* 1987;82:422-3.
 17. Wright S, Sanders TAB. Adipose tissue fatty acid composition in patients with atopic eczema. *Br J Nutr* (in press).
 18. Wright S, Bolton C. Breast milk fatty acids in mothers of children with atopic eczema. *Br J Nutr* 1989;62:693-7.
 19. Galli E, Picardo M, De Luca C, et al. Essential fatty acids in cord blood lymphocytes of infants at risk for atopy. *Pediatr Res* 1989;26: 519 (abstr).
 20. Oliwiecki S, Burton JL, Elles K, Horrobin DF. Levels of essential and other fatty acids in plasma and red cell phospholipids from normal controls and patients with atopic eczema. *Acta Derm Venereol* 1990;71:224-8.
 21. Lovell CR, Burton JL, Horrobin DF. Treatment of atopic eczema with evening primrose oil. *Lancet* 1981;1:278.
 22. Wright S, Burton JL. Oral evening primrose seed oil improves atopic eczema. *Lancet* 1982;2:1120-2.
 23. Schalin-Karrila M, Mattila L, Jansen CT, et al. Evening primrose oil in the treatment of atopic eczema: effect on clinical status, plasma phospholipid fatty acids and circulating blood prostaglandins. *Br J Dermatol* 1987;117:11-9.
 24. Guenther L, Wexler D. Efamol in the treatment of atopic dermatitis. *J Am Acad Dermatol* 1987;17:860 (letter).
 25. Morse PF, Horrobin DF, Manku MS, Stewart JCM. Meta-analysis of placebo-controlled studies of the efficacy of gamma-linolenic acid in the treatment of atopic eczema. *Br J Dermatol* 1989;121:75-90.
 26. Stewart JCM, Morse PF, Moss M. Treatment of severe and moderately severe atopic dermatitis with evening primrose oil (Epogam): a multicentre study. *J Nutr Med* 1991;2:9-15.
 27. Marshall RJ, Evans RW. Measurement of the effects of essential fatty acids on human skin smoothness. In: Horrobin DF, ed. *Omega-6 essential fatty acids: pathophysiology and roles in clinical medicine*. New York: Alan Liss, 1990:81-98.
 28. Nissen HP, Wehrmann W, Kroll U, Kreyser HW. Influence of polyunsaturated fatty acids on the plasma phospholipids of atopic patients. *Fat Sci Technol* 1988;7:247-88.
 29. Meigel W. Treatment of atopic dermatitis. *Z Hautkr* 1986;61:473-8.
 30. Bordoni A, Biagi P, Masi M, et al. Evening primrose oil (Efamol) in the treatment of children with atopic eczema. *Drugs Exp Clin Res* 1987;14:291-7.
 31. Heddle R, Gibson RG. A controlled trial of evening primrose oil and safflower oil in children with atopic eczema. *Proc Nutr Soc Australia* (in press).
 32. Peifer JJ, Holman RT. Essential fatty acids, diabetes and cholesterol. *Arch Biochem Biophys* 1955;57:520-1.
 33. Mercuri O, Peluffo RO, Brenner RR. Depression of microsomal desaturation of linoleic to gamma-linolenic acid in the alloxan diabetic rat. *Biochim Biophys Acta* 1966;116:407-11.
 34. Brenner RR, Peluffo RO, Mercuri O, Restelli MA. Effect of arachidonic acid in the alloxan diabetic rat. *Am J Physiol* 1968;215:63-9.
 35. Faas FH, Carter WJ. Altered fatty acid desaturation and microsomal fatty acid composition in streptozotocin diabetic rat. *Lipids* 1980;15: 953-61.
 36. Friedman N, Gellhorn A, Benjamin W. Synthesis of arachidonic acid from linoleic acid in vivo in diabetic rats. *Israel J Med Sci* 1966;2:677-82.
 37. Huang Y-S, Horrobin DF, Manku MS, Mitchell J, Ryan MA. Tissue phospholipid fatty acid composition in the diabetic rat. *Lipids* 1984;19:367-70.
 38. Poisson J-P. Comparative in vivo and in vitro study of the influence of experimental diabetes on rat liver linoleic acid 6- and 5-desaturation. *Enzyme* 1985;34:1-14.
 39. Van Doormaal JJ, Idema IG, Muskiet FAJ, et al. Effects of short term high dose intake of evening primrose oil on plasma and cellular fatty acid compositions, alpha-tocopherol levels and erythropoiesis in normal and type I (insulin-dependent) diabetic men. *Diabetologia* 1988;31:576-84.
 40. Tilvis RS, Miettinen TA. Fatty acid composition of serum lipids, erythrocytes and platelets in insulin-dependent diabetic women. *J Clin Endocr Metab* 1985;61:741-5.
 41. Arisaka M, Arisaka O, Yamashiro Y. Fatty acid and prostaglandin metabolism in children with diabetes mellitus II. The effect of evening primrose oil supplementation on serum fatty acid and plasma prostaglandin levels. *Prostaglandins Leukotr Med* 1991;43:197-201.
 42. Jones BD, Carter RD, Mann JI. Indirect evidence of impairment of platelet desaturase enzymes in diabetes mellitus. *Horm Metab Res* 1986;18:341-4.
 43. Tilvis RS, Helve E, Miettinen TA. Improvement of diabetic control by continuous subcutaneous insulin infusion therapy changes fatty acid composition of serum lipids and erythrocytes in type I (insulin-dependent) diabetes. *Diabetologia* 1986;29:690-4.
 44. Patterson JW. Effect of a high fat fructose and casein diet on diabetic cataracts. *Proc Soc Exp Biol Med* 1955;90:706-8.
 45. Patterson JW, Patterson ME, Kinsey VE, Reddy DVN. Lens assays on diabetic and galactosemic rats receiving diets that modify cataract development. *Invest Ophthalmol* 1965;4:98-103.
 46. Hutton JC, Schofield PJ, Williams JF, Regtop HL, Hollows FC. The effect of an unsaturated fat diet on cataract formulation in streptozotocin-induced diabetic rats. *Br J Nutr* 1976;36:161-77.
 47. Kinsell LW, Walker G, Michaels GD, Olson FE. Dietary fats and the diabetic patient. *N Engl J Med* 1959;261:431-4.
 48. King RC, Dobree JH, Kok DA, Foulds WS, Dangerfield WG. Exudative diabetic retinopathy: spontaneous changes and effect of a corn oil diet. *Br J Ophthalmol* 1963;47:666-72.
 49. Houtsmuller AJ. Significance of linoleic acid in the metabolism and therapy of diabetic retinopathy. *World Rev Nutr Diet* 1982;39:85-123.
 50. Howard-Williams J, Patel P, Jelfs R et al. Polyunsaturated fatty acids and diabetic retinopathy. *Br J Ophthalmol* 1985;69:15-8.
 51. Horrobin DF. The roles of essential fatty acids in the development of diabetic neuropathy and other complications of diabetes mellitus. *Prostaglandin Leukotr Med* 1988;31:181-97.
 52. Horrobin DF. Essential fatty acids, psychiatric disorders and neuropathies. In: Horrobin DF, ed. *Omega-6 essential fatty acids: Pathophysiology and roles in clinical medicine*. New York: Alan Liss, 1990:305-19.
 53. Dyck PJ, Thomas PK, Asbury AK, Winegard AI, Porte D, eds. *Diabetic neuropathy*. Philadelphia: WB Saunders, 1987.
 54. Jamal GA, Carmichael H. The effect of gamma-linolenic acid on human diabetic peripheral neuropathy: a double blind placebo-controlled trial. *Diabetic Med* 1990;7:319-23.
 55. Julu POO. Gamma-linolenic acid: a novel remedy for diabetic neuropathy in experimental animals. In: Horrobin DF, ed. *Omega-6 essential fatty acids: pathophysiology and roles in clinical medicine*. New York: Alan Liss 1990:465-76.
 56. Julu POO. Essential fatty acids prevent slowed nerve conduction in streptozotocin diabetic rats. *J Diabetic Complications* 1988;2:185-8.
 57. Cameron NE, Cotter MA, Robertson S. Essential fatty acid diet supplementation. Effects on peripheral nerve and skeletal muscle function and capillarization in streptozotocin-induced diabetic rats. *Diabetes* 1991;40:532-9.
 58. Tomlinson DR, Robinson JP, Compton AM. The effects of gamma-linolenic acid treatment on motor nerve conduction velocity and axonal transfer of substance P in diabetic rats. In: Horrobin DF, ed.

- Omega-6 essential fatty acids: pathophysiology and roles in clinical medicine. New York: Alan Liss, 1990:457-63.
59. Tomlinson DR, Robinson JP, Compton AM, Keen P. Essential fatty acid treatment—effects on nerve conduction, polyol pathway and axonal transfer in streptozotocin diabetic rats. *Diabetologia* 1989;32:655-9.
 60. Keen H, Payan J, Allawi J, et al. Treatment of diabetic neuropathy with γ -linolenic acid. *Diabetes Care* 1993;16:8-15.
 61. Williams R, Broughton M. A pilot study of gamma-linolenic acid in diabetic retinopathy. In: Horrobin DF, ed. *The treatment of diabetic neuropathy: a new approach*. Edinburgh: Churchill Livingstone, 1992:131-5.
 62. Horrobin DF, ed. *Omega-6 essential fatty acids: pathophysiology and roles in clinical medicine*. New York: Alan Liss, 1990.
 63. Horrobin DF. Gamma Linolenic acid. *Rev Contemp Pharmacother* 1990;1:1-41.
 64. Horrobin DF. Nutritional and metabolic importance of gamma-linolenic acid. *Prog Lipid Res* 1992;31:163-94.

Discussion

Michael A Crawford: Thank you very much, David, indeed, for that important and most interesting contribution. I think that the reason why nobody has picked this up over these years (apart from yourself and the Unilever people in Vlaardingen) is fairly obviously that the major thrust in biomedical research in Europe since the Second World War has been in the pharmaceutical business, where the rewards in terms of capital gain have been so phenomenal. This has turned and distorted the priorities of the research councils, certainly in the United Kingdom, where a very large bulk of the research budgets is devoted to those aspects of biology that have a direct pharmacological and curative approach. As a consequence of that particular motivation, nutritional research has been hopelessly underfunded, particularly where one is dealing with disorders of the nervous system. The problem with the nervous system is that it is very carefully protected from its external environment, which includes what is circulating in the blood. That means that if you have deficits or distortions in the nervous system, they tend to be recycled and they are protected and held in place. So it does take a considerable period of time to sort those things out, and it is very encouraging to see these data coming forward with these long-term studies and showing these benefits.

Antoine J Vergoesen: Dr Horrobin, last year, we had a short correspondence on this topic and I enjoy the opportunity to continue this discussion now. I realize, however, that it will be more or less "mission impossible," because of the tremendous amount of data presented in your lecture. Because the essence of our discussion concerns to what extent γ -linolenic acid (18:3, n-6, 9, 12, all *cis*) might be superior to the widely available linoleic acid (18:2, n-6, 9, all *cis*), the selection of the placebo (control) substance is very important. If I understood you correctly, in two studies with type 1 diabetic patients you used linoleic acid as a control and you observed γ -linolenic acid to be superior in these two experiments. However, I should like to stress that in these two studies, a serious insulin deficiency existed, a situation in which a block in the desaturation of linoleic to γ -linolenic acid exists indeed. Consequently, a favorable effect of the dietary administration of γ -linolenic acid might be expected. However, human patients with diabetes mellitus type 2 (a relative insulin deficiency caused by obesity and inadequate insulin receptors) are treated such that an excess of circulating insulin is more likely to exist than a reduced insulin concentration. My question is, to what extent does your claim about a superiority of γ -linolenic acid over linoleic acid hold in this latter, much more common, situation? In my expectation, it is very unlikely that an extra beneficial effect of γ -linolenic acid will be observed over what can be achieved already with the consumption of the

generally recommended diet with 10 en% or less saturated fatty acids and at least 10 en% of linoleic acid. Such a diet has been used before by Houtsmuller and coworkers in their successful 11-y prospective trial in patients with type 2 diabetes mellitus [Houtsmuller AJ, van Hal-Ferwerda J, Zahn KJ, Henkes HE. Favourable influences of linoleic acid on the progression of diabetes mellitus. *Prog Lipid Res* 1981;20:377-86]. Because evening primrose oil, apart from 8-10% of γ -linolenic acid, also contains some 70% linoleic acid, the selection of a control oil with a similar linoleic acid content is necessary before conclusions about γ -linolenic acid are justified.

My other question is about the safety approach of this concept. I remember that about 20 years ago, Prof Boldingh suggested to us at Unilever Research in Vlaardingen to use evening primrose oil to improve the quality of dietary products to prevent atherosclerosis and/or to cure some of the symptoms. At that time, a study was performed at an independent laboratory in Edinburgh, comparing γ -linolenic acid and linoleic acid, both in relation to thrombotic episodes. Our expectation was that γ -linolenic acid might be much more useful in this case than is linoleic acid. Actually, the opposite was observed, which raises the issue of potential hazards in bypassing the physiologically active negative feedback control exerted by arachidonic acid on the desaturation and elongation of linoleic acid. Can you comment on this, please?

David F Horrobin: Sure. First, in relation to the type of diabetes: obviously, there are type 1, insulin-dependent, and type 2, non-insulin-dependent, diabetes. I didn't really have time to show all the details, but, in fact, approximately half the patients in the trial were insulin-dependent and half the patients were non-insulin-dependent. Both types, by the way, get neuropathy equally: there is really no difference in neuropathy between the two varieties. Both types responded equally to the treatment; there was no difference in the clinical response between the insulin-dependent and the non-insulin-dependent diabetics. They both responded very well to the γ -linolenic acid. Secondly, concerning the relationship between linoleic acid and γ -linolenic acid: I have no doubt that if you give enough linoleic acid, it will be as effective as γ -linolenic acid. The problem is how much you have to give. In the animal studies, it is very clear that whereas γ -linolenic acid very readily does reverse the abnormalities in nerve conduction, linoleic acid does not do so, unless you give astronomical amounts, and even then it is less effective than γ -linolenic acid.

Vergoesen: What do you mean by astronomical amounts?

Horrobin: Even at an intake 20% by diet weight, which is roughly 40% by Joules, you do not get the same restoration of nerve conductivity as you do by giving 0.5% by weight of γ -linolenic

acid. So, there is a considerable difference in the efficacy of linoleic acid and γ -linolenic acid in these animal studies. In the human studies, I am quite sure, as Houtsmuller demonstrated, that if you give enough linoleic acid you will get very substantial benefit. The problem is that many patients do not seem to like these very-high-linoleic acid diets.

Vergroesen: May I comment on that, shortly? The diet used by Houtsmuller et al in the experimental group was completely identical to the generally recommended, safe diet for the general public. It was not an extreme diet.

Horrobin: No, I don't think that the Houtsmuller study provided an extreme diet, but the fact is that many research groups, particularly in the UK, have tried to repeat the studies and found that they have not been able to persuade patients to stick to these diets. I think good results are perfectly possible, provided you are very dedicated and successful at getting patients to stick to these diets. In practice, however, many diabetic patients, just like other patients and indeed like all of us, are not really dedicated to sticking to a dietary regime over a long period of time. Most patients seem to find it a lot easier to take a supplement of a few hundred milligrams of γ -linolenic acid per day rather than to modify their diet over a long period of time. This clearly presents a practical problem, which is illustrated by the fact that, although the clinical results of Houtsmuller et al were truly convincing, almost no diabetologist in the world recommends this diet to patients. If you ask the diabetologists why they don't recommend this diet, they reply that the patients have difficulties

in complying with the diet over a longer period of time. However, if companies succeed in making palatable linoleic acid-rich diets, we might have a different situation. But the fact is that the results of the Houtsmuller study have not actually been incorporated into clinical practice, largely because of the practical problems.

Let's now move to the toxicology issue. We have done complete toxicological evaluations of γ -linolenic acid. We performed a 1-y rat study and a 1-y dog study, we investigated carcinogenesis in rats and mice, and essentially there is no toxicity of γ -linolenic acid [Everett DJ, Greenough RJ, Perry CJ, McDonald P, Bayliss P. Chronic toxicity studies of Efamol evening primrose oil in rats and dogs. *Med Sci Res* 1988;16:863-4. Everett DJ, Perry CJ, Bayliss P. Carcinogenicity studies of Efamol evening primrose oil in rats and mice. *Med Sci Res* 1988;16:865-6]. We also addressed the thrombotic issue, looking at thrombosis following a condition called angioplasty. Many of you will be familiar with the fact that blood vessels that have been clogged up can be unclogged by putting a balloon into the artery and, by inflating, the obstruction can be removed. This procedure is called angioplasty, but the problem is that there is $\approx 30\%$ reocclusion of the treated artery within 1 y. We are just completing a study at Dundee University Medical School, where we are taking patients who are undergoing femoral angioplasty and giving them either placebo or γ -linolenic acid. In the placebo group, the reocclusion rate within a year is $\approx 30\%$, in the γ -linolenic acid group the reocclusion rate within 1 y is $\approx 12\%$ (unpublished results). So there is a considerable reduction in reocclusion following angioplasty in the patients who were given γ -linolenic acid.

