

# Evening primrose oil and borage oil in rheumatologic conditions<sup>1-3</sup>

Jill JF Belch and Alexander Hill

**ABSTRACT** Diets rich in arachidonic acid (20:4n-6) lead to the formation of 2-series prostaglandins (PGs) and 4-series leukotrienes (LTs), with proinflammatory effects. Nonsteroidal anti-inflammatory drugs are used in rheumatoid arthritis to inhibit cyclooxygenase (prostaglandin-endoperoxide synthase), thereby decreasing production of 2-series PGs. Lipoxygenase activity remains intact, however, allowing LT production (eg, synthesis of LTB<sub>4</sub>, a potent inflammatory mediator) to continue. Altering the essential fatty acid (EFA) content of the diet can modify some of these effects. Ingestion of a diet rich in evening primrose oil elevates concentrations of dihomo- $\gamma$ -linolenic acid (DGLA; 20:3n-6), which results in the production of 1-series PGs, eg, PGE<sub>1</sub>. DGLA itself cannot be converted to LTs but can form a 15-hydroxyl derivative that blocks the transformation of arachidonic acid to LTs. Increasing DGLA intake may allow DGLA to act as a competitive inhibitor of 2-series PGs and 4-series LTs and thus suppress inflammation. The results of in vitro and animal work evaluating EFAs in inflammatory situations are encouraging, which has stimulated clinical workers to evaluate these compounds in rheumatoid arthritis. Several well-controlled, randomized clinical studies have now been completed in which various EFAs were evaluated as treatments. The results of most of these studies suggest some clinical benefit to these treatments; these data are reviewed here. *Am J Clin Nutr* 2000;71(suppl):352S-6S.

**KEY WORDS** Essential fatty acids, evening primrose oil, borage oil, rheumatoid arthritis, Raynaud phenomenon, Sjögren syndrome, dihomo- $\gamma$ -linolenic acid

## INTRODUCTION

### Eicosanoid formation

The essential fatty acids (EFAs) have unique roles as precursor molecules of chemical regulators of inflammatory cell function (1). These regulators are the prostaglandins (PGs) and the leukotrienes (LTs), compounds synthesized and released by almost every tissue in the body and that participate in many biological functions, including the inflammatory and immune processes. The derivation of PGs and LTs from their precursor EFAs is illustrated in **Figure 1**. Dihomo- $\gamma$ -linolenic acid (DGLA; 20:3n-6) leads to the formation of the 1-series PGs, arachidonic acid (20:4n-6) leads to the 2-series PGs, and eicosapentaenoic acid (20:5n-3) leads to the 3-series PGs. Most research centers on arachidonic acid, the precursor of the 2-series PGs and the 4-series LTs.

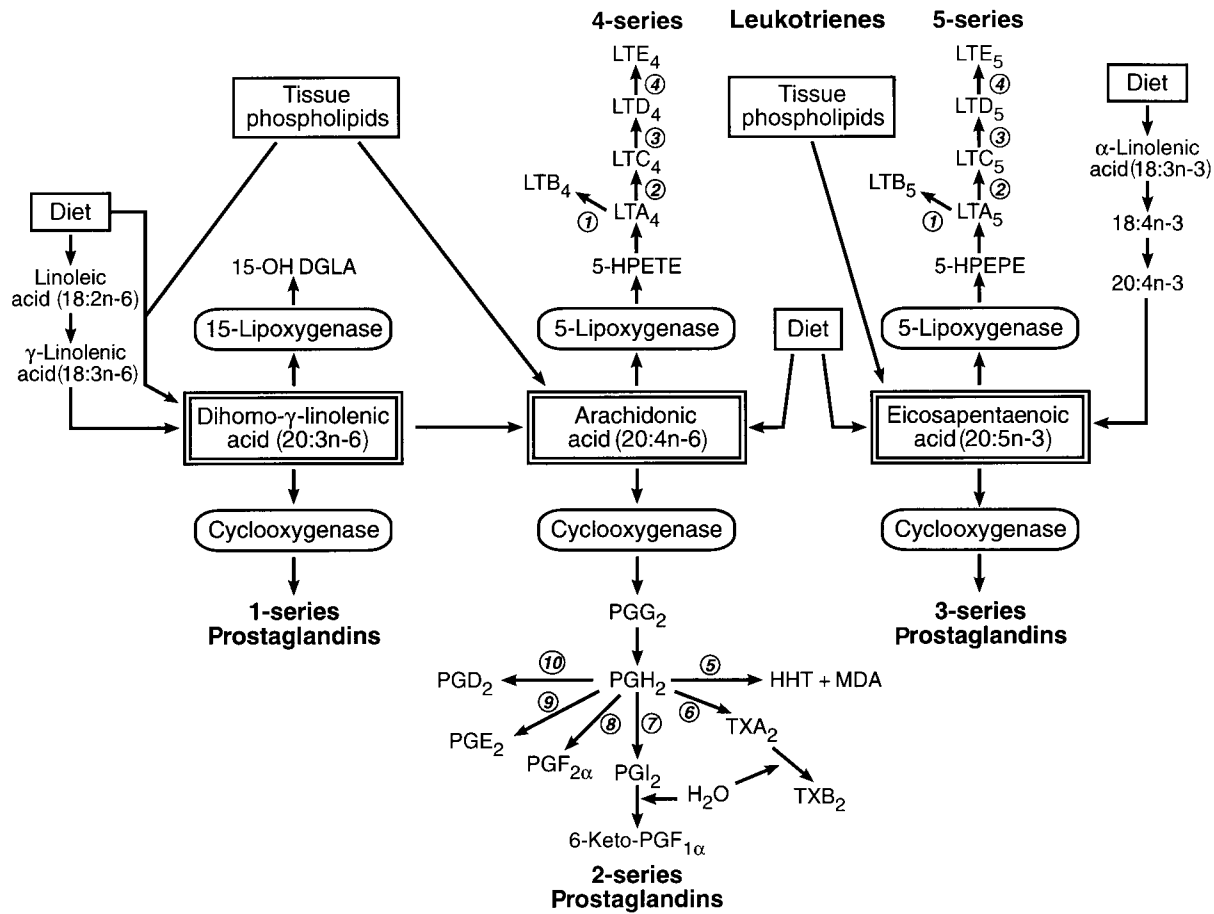
Altering the EFA content of the diet or administering different EFAs as supplements can modify the production of the various PGs and LTs. By altering the substrate EFA, for example, the ingestion of a diet rich in evening primrose oil (EPO) or borage oil (starflower oil) elevates DGLA concentrations, resulting in an increase in the 1-series PGs, eg PGE<sub>1</sub> (2). In common with all PGs, PGE<sub>1</sub> can induce the cardinal signs of inflammation: redness, edema, pain, heat, and loss of function. In contrast, however, the action of PGE<sub>1</sub> on the inflammatory cells, ie, the polymorphonuclear leukocytes, is mostly inhibitory (3). PGE<sub>1</sub> increases intracellular cyclic AMP (cAMP) and it is this increase in polymorphonuclear leukocyte cAMP that reduces the release of lysosomal enzymes, reduces polymorphonuclear leukocyte chemotaxis, and reduces the margination and adherence of leukocytes in the blood vessels. Similarly, the effect of PGE<sub>1</sub>s on lymphocytes is thought to be inhibitory (4). Exogenous addition of PGE<sub>1</sub> inhibits both in vitro function of lymphocytes and in vivo responses mediated by lymphocytes. It has been suggested that PGE<sub>1</sub> has a negative feedback role in chronic inflammation, initially aiding in the development of the cardinal signs of inflammation but later suppressing inflammation, and that this antiinflammatory effect might be useful in a disease characterized by inflammation such as rheumatoid arthritis.

A further benefit of a diet rich in compounds containing  $\gamma$ -linolenic acid (GLA; 18:3n-6), which is metabolized to DGLA, is the inhibitory effect of GLA on LT synthesis. LTB<sub>4</sub> is one of the major metabolic products of arachidonic acid metabolism and activates the leukocytes responsible for chemokinesis, chemotaxis, adherence, and granulation. Additionally, LTB<sub>4</sub> enhances the presentation of C<sub>3b</sub> receptors. DGLA itself cannot be converted to LTs but can form a 15-hydroxyl derivative that blocks the transformation of arachidonic acid to LTs (5). Additionally, a 13(S)-hydroxy-9(Z),11(E)-octadecadienoic acid product may be formed that may also have antiinflammatory effects. Thus, increased intake of GLA may suppress inflammation through the metabolism of GLA to DGLA and thus competitive inhibition of the 2-series PGs and 4-series LTs. Much in vitro animal and human

<sup>1</sup>From the Department of Medicine, Ninewells Hospital and Medical School, Dundee, United Kingdom.

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<sup>3</sup>Address reprint requests to JF Belch, Department of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, United Kingdom. E-mail: j.j.f.belch@dundee.ac.uk.



**FIGURE 1.** Metabolism of essential fatty acids to leukotrienes (LTs), prostaglandins (PGs), and thromboxanes (TXs). The precursor fatty acids are from the diet, are formed from dietary fatty acids by successive fatty acid desaturase and fatty acid elongase enzymes, or are released from tissue phospholipids by phospholipase A<sub>2</sub>. For simplicity, only the PG metabolites of the 2-series are shown; conversions are similar for the other series. Substrates from each series compete for the same enzyme systems, which are numbered in the figure as follows: 1) leukotriene-A<sub>4</sub> hydrolase, 2) glutathione transferase, 3) γ-glutamyltransferase, 4) Cys-Gly dipeptidase, 5 and 6) thromboxane-A synthase, 7) prostaglandin-I synthase, 8) prostaglandin-F synthase, 9) prostaglandin-E synthase, and 10) prostaglandin-D synthase. Cyclooxygenase, prostaglandin-endoperoxide synthase; HHT, 12-hydroxy-5,8,10-hepatadecatrienoic acid; 5-HPEPE, 5-hydroperoxy-6,8,11,14,17-pentaenoic acid; 5-HPETE, 5-hydroperoxy-6,8,11,14-teraenoic acid; 5-lipoxygenase, arachidonate 5-lipoxygenase; 15-lipoxygenase; arachidonate 15-lipoxygenase; MDA, malondialdehyde; 15-OH DGLA, 15-hydroxydihomo-γ-linolenic acid.

work suggests that such a modification of PG and LT production does occur (2, 6, 7), as reviewed elsewhere in this supplement (8).

**Membrane effects**

Although the metabolism of various EFAs to PGs and LTs is important, one must remember that EFAs are key components of cell membranes and that altering the EFA profile may also modify inflammatory-cell behavior through membrane effects. For example, cell membrane flexibility is dependent on fatty acid content and an increase in the amount of saturated fatty acids within the macrophage membrane will reduce its endocytic activity (9).

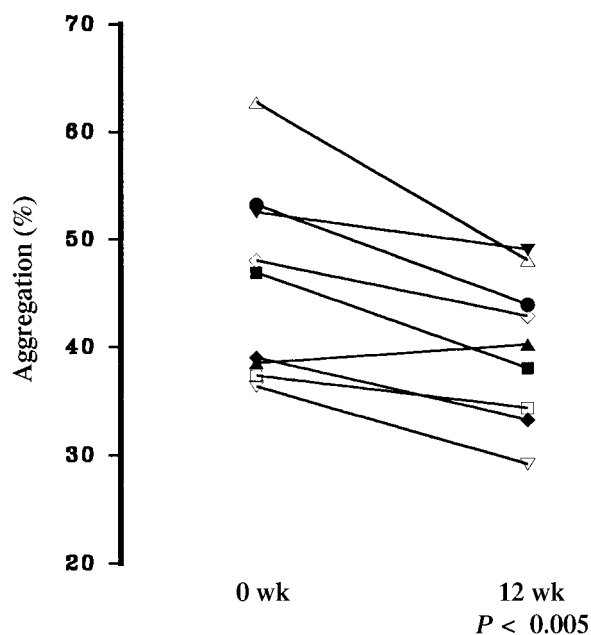
**Cell adhesion molecules**

Leukocytes flow in the central area of the bloodstream. When activated, they migrate to the side of the blood vessel and then roll along the blood vessel until immobilized. After they are immobilized, the leukocytes pass through the endothelium into the tissue, where they can mediate the inflammatory response. The ability of polymorphonuclear leukocytes to roll on and adhere to the endothe-

lium is mediated by various cell adhesion molecules. One of these cell adhesion molecules, E-selectin, is presented only on endothelial tissue. After the leukocyte migrates into the tissue, E-selectin is no longer required and is shed into the circulation. Interleukin 8 is responsible for leukocyte activation; thus, inhibition of its formation by GLA supplementation would also be expected to reduce polymorphonuclear leukocyte function. In a preliminary pilot study, we evaluated the effect of GLA on leukocyte aggregation in whole blood in response to *N*-formyl-methionyl, leucinyll, and phenylalanyl tripeptide and found that leukocyte aggregation was reduced after the 12-wk GLA treatment period (Figure 2, Table 1). A larger study is underway to investigate the effect of GLA supplementation on cell adhesion molecules.

**Endothelial effects**

Another potential mechanism whereby GLA and DGLA mediate their beneficial effects is through the fibrinolytic process. Fibrin is deposited in excess in rheumatoid joints and we have shown that the fibrinolytic process is inhibited in these



**FIGURE 2.** Improvement (Student's paired *t* test) in leukocyte aggregation in response to 0.1 mol *N*-formylmethionyl, leucyl, and phenylalanyl tripeptide/L before and after 12 wk of supplementation with dihomo- $\gamma$ -linolenic acid in 9 healthy adults.

rheumatoid arthritis patients. In a group of subjects with Raynaud phenomenon secondary to rheumatologic conditions, we showed that a 12-wk course of supplementation with GLA enhanced fibrinolysis through an increase in tissue-type plasminogen activator, resulting in an increased amount of fibrin degradation products in the blood (Table 1).

In summary, manipulation of the parent EFA can modify inflammation in several ways. These include altered production of eicosanoids, effects on membranes, and effects on fibrosis and scarring.

#### Rheumatologic conditions in which EFA treatment has been evaluated

Kremer (14) reviewed the use of *n*-3 fatty acids in rheumatoid arthritis; thus, this article deals only with the effects of *n*-6 and combined *n*-6 and *n*-3 fatty acid supplementation. It is important to appreciate that each type of EFA can interfere with the metabolism of the other. An excess of *n*-6 EFAs will reduce the metabolism of  $\alpha$ -linolenic acid, possibly leading to a deficit of its metabolites, including eicosapentaenoic acid. Similarly, diets rich in *n*-3 EFAs effectively inhibit the metabolism of *n*-6 EFAs (15).

Most studies of GLA supplementation have been performed in subjects with rheumatoid arthritis (16), but 2 conditions associated with rheumatoid arthritis have also been studied: Raynaud phenomenon and Sjögren syndrome. Additionally, another arthritic disorder, psoriatic arthritis, has also been evaluated. All these will be reviewed; our own experience with GLA supplementation is shown in Table 1.

#### Raynaud phenomenon

Raynaud phenomenon is characterized by digital vasospasm, which produces the classic triphasic color change of blanching

(due to vascular spasm), cyanosis (due to deoxygenation of static venous blood), and rubor (reflecting the reactive hyperaemia of return of flow) (17). In a disease characterized by vascular spasms, enhancing the production of vasodilatory PGs by manipulating EFAs is an attractive possibility. Raynaud phenomenon is also associated with enhanced platelet aggregation (18), decreased red blood cell deformability, increased leukocyte aggregation and release (19), and diminished fibrinolysis (20), all of which might be expected to be ameliorated by supplementation with GLA.

We studied the effect of 12 capsules of EPO daily on the manifestations of Raynaud phenomenon (11). This dosage provided a total of 540 mg GLA. Twenty-one patients received a 2-wk course of run-in placebo medication (liquid paraffin); thereafter, 11 received EPO for 8 wk while 10 patients received placebo. As the weather worsened from autumn to winter, the placebo group experienced significantly more vasospastic attacks than did the EPO group and these attacks lasted much longer (Table 1). Visual analogue scales assessing the severity of attacks and coldness of the hands improved in the EPO group compared with the placebo group. Blood tests showed some antiplatelet effect of the drug, as expected. Interestingly, similar findings were described by Ralph et al (21) in a study of fish-oil supplementation of subjects with Raynaud phenomenon. Disappointingly, however, no further studies in this area have been published. Although these studies were of a standard type used to assess Raynaud phenomenon in the 1980s, current requirements would necessitate that larger numbers of subjects be studied over a longer period of time. Such studies have not been forthcoming; thus, we cannot conclusively recommend EPO treatment for patients with Raynaud phenomenon.

#### Sjögren syndrome

Sjögren syndrome is a common autoimmune, chronic inflammatory disorder that is often associated with rheumatoid arthritis (22). GLA concentrations have been noted to be reduced in patients with Sjögren syndrome (23) and replacement via treatment with Efamol (Scotia Pharmaceuticals Ltd, Stirling, United Kingdom) has been attempted. In the first such study (24), 36 patients were evaluated in a randomized, double-blind, crossover fashion. Unfortunately, only a 1-wk washout phase was used, a design we now know to be inappropriate when evaluating EFA therapy. Nevertheless, the dosage of 3 capsules Efamol/d (500-mg capsules containing 73% linoleic acid and 9% GLA) and 3 tablets of Efavit (containing 125 mg vitamin C, 25 mg pyridoxine, 25 mg niacin, and 5 mg zinc sulfate; Scotia Pharmaceuticals Ltd) twice daily improved results on the Schirmer tear test over the treatment period compared with placebo. (The Schirmer tear test is a measurement of tear fluid production in which enhanced tear formation represents improvement.) The second study evaluated 28 patients (25). In this study, Efamol was given for 8 wk at a dosage of 6 capsules/d. Ocular scores, which included evaluation of the Schirmer tear test, improved during Efamol treatment compared with pretrial values but not compared with the placebo group. Once again, it is interesting that this work, which was carried out in the 1980s, has not been taken further. Enough time has passed for larger, conclusive studies to have been completed and it is disappointing that this is not the case. Thus, in the absence of further data, this treatment cannot be recommended to patients with Sjögren syndrome.

#### Psoriatic arthritis

Interest in treating psoriatic arthritis sufferers with GLA-rich supplementation developed following studies of this skin

**TABLE 1**

Effect of supplementation with  $\gamma$ -linolenic acid in healthy and diseased subjects (see text for details)

Subject group	Clinical index	Response	Reference
Healthy	Leukocyte aggregation	Decrease	10
Raynaud phenomenon	Vasospasm duration	Decrease	11
Reynaud phenomenon	Vasospasm severity	Decrease	11
Rheumatoid arthritis	Pain severity	Decrease	12
Rheumatoid arthritis	Fibrinolysis	Decrease	12
Psoriatic arthritis	Pain severity	No change	13

disease in which benefit was shown by treatment with fish oils (26, 27). Additionally, in one of these studies benefits of n-3 fatty acid treatment of psoriatic skin disease were reported (27). Disappointingly, however, in a double-blind, placebo-controlled study of 38 patients (13), no obvious benefits of GLA supplementation were found. In particular, the articular index remained the same in both the placebo and the treatment groups, as did consumption of nonsteroidal antiinflammatory drugs (Table 1). The dosage of 12 capsules/d may have been too low to produce benefit because more profound effects in rheumatoid arthritis are found with higher doses (28).

### Rheumatoid arthritis

Kremer (14) has reviewed the effects of n-3 fatty acid supplementation in rheumatoid arthritis. For the reasons outlined above, it might be expected that n-6 fatty acid supplementation or a combination of n-3 and n-6 fatty acid supplementation might also be useful in this group of patients. The literature is difficult to review, however, because inappropriate study designs were used when evaluating GLA in rheumatoid arthritis. This is not necessarily the fault of the investigators concerned, but reflects merely the state of the art at the time these studies were carried out. In one of the first studies, Brown et al (29) evaluated EPO in 19 patients with rheumatoid arthritis. The dosage selected was 700 mg/d of oil containing 70% linoleic acid and 7% GLA. We now know that this dosage is unlikely to produce benefit and indeed the results of this study were negative. In another study by Hansen et al (30), although there was a trend for improvement in the EPO group, a low dosage regimen was used. Additionally, in both these studies, the time period evaluated was only 3 mo; we now know that  $\geq 3$ -4 mo is required for therapeutic benefits to become apparent.


Another problem in studies of rheumatoid arthritis is the selection of an active placebo. Brzeski et al (31) evaluated 40 rheumatoid arthritis patients who received a 6-mo treatment of either EPO or placebo. The placebo selected, however, was olive oil, which may also have antiinflammatory effects. Unsurprisingly, therefore, there were significant results in both groups. Improvements in morning stiffness and a trend to decreased articular index were reported in the EPO group, whereas in the placebo group, there was a significant reduction in articular index and a trend to reduced morning stiffness. Furthermore, between 40% and 50% of the patients studied were taking disease-modifying agents (second-line therapy) for their rheumatoid arthritis. The mechanism of action of several such agents is mediated partially through PG and LT production; thus, it is inappropriate to evaluate these patients when only a modest dose of GLA was given (540 mg GLA/d).

In our own study (12), we excluded patients requiring second-line therapy, treated the patients for 12 mo (with a 3-mo placebo washout phase), and used liquid paraffin as the placebo. We showed a significantly lower requirement for nonsteroidal antiinflammatory drugs in subjects given 12 capsules EPO/d (540 mg GLA) and in those given an EPO-fish oil mix (450 mg GLA, 240 mg eicosapentaenoic acid) than in the placebo group (Table 1). Use of liquid paraffin as a placebo allowed us to attenuate what is normally a considerable placebo effect in this group of subjects. Unfortunately, with the higher doses of EFAs currently being studied (28), liquid paraffin is probably not an appropriate placebo.

The choice of an active placebo remains a problem. In our study of fish oil in rheumatoid arthritis (32), we used air-filled capsules as a placebo. At the end of the study, we contacted all patients by letter and only 1 of 30 placebo subjects had realized that the capsules were empty. Hence, air-filled capsules may be an appropriate choice for future studies. Other alternatives may include using the recently registered, nonabsorbable fat olestra, but this would not have the same energy value as the active treatment, or encapsulating the standard fat content of the diet in the country under study. The problem with the latter option is that it could increase saturated fat intake, which may be unethical (33).

Zurier et al (28) evaluated a high dose of GLA (2.8 g/d as the free fatty acid) against a placebo of sunflower seed oil. In this study, GLA treatment resulted in a statistically significant reduction in the signs and symptoms of rheumatoid arthritis disease activity. Fifty-six patients received a 6-mo course of either GLA or placebo followed by a single, blind, 6-mo study in which all patients received GLA. During the second 6 mo, disease activity improved in both groups. The GLA dosage used in this study was well tolerated. Further controlled studies of this dosage in rheumatoid arthritis are warranted.

### CONCLUSIONS

Dietary manipulation of EFAs or supplementation with therapeutic doses of EFAs may be effective for treating inflammatory disorders (34, 35). The effects of n-6 EFAs have been poorly studied to date, however, and results are inconclusive for use of EFAs in the treatment of Raynaud phenomenon and Sjögren syndrome. More convincing evidence exists in support of EFA use in rheumatoid arthritis; the study by Zurier et al (28) in which a high dose of GLA was evaluated is particularly interesting. It is possible that a new family of EFA antirheumatic drugs will soon be available. However, this is dependent solely on the completion of well-designed clinical studies that are double-blind, contain adequate power, and do not use an active placebo. 

### REFERENCES

1. Belch JF. Eicosanoids and rheumatology: inflammatory and vascular aspects. *Prostaglandins Leukot Essent Fatty Acids* 1989;36:219-34.
2. Manku MS, Morse N, Belch JF. Effects of gamma-linolenic acid supplementation on plasma essential fatty acids. *Prog Lipid Res* 1986;25:469-73.
3. Weissmann G, Smolen JE, Kirchak H. Prostaglandins and inflammation: receptor/cyclase coupling as an explanation of why PGEs and PGI<sub>2</sub> inhibit functions of inflammatory cells. In: Samuelsson B, Ramwell PW, Paoletti R eds. *Advances in prostaglandin and thromboxane research*. New York: Raven Press, 1980:1637-53.
4. Rogers TJ. The role of arachidonic acid metabolites in the function of murine suppressor cells. In: Goodwin JS, ed. *Prostaglandins and immunity*. Boston: Martinus Nijhoff, 1985:954-8.



5. Voorhees JJ. Leukotrienes and other lipoxygenase products in the pathogenesis and therapy of psoriasis and other dermatoses. *Arch Dermatol* 1983;111:541-7.
6. Jantti J, Nikkari T, Solskivi T, Vapaatalo H, Isomaki H. Evening primrose oil in rheumatoid arthritis: changes in serum lipids and fatty acids. *Ann Rheum Dis* 1989;48:124-7.
7. Oxholm P, Pedersen BK, Horrobin DF. Natural killer cell functions are related to the cell membrane composition of essential fatty acids: differences in healthy persons and patients with primary Sjögren's syndrome. *Clin Exp Rheumatol* 1992;10:229-34.
8. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 2000;71(suppl):343S-8S.
9. Meade CJ, Mertin J. Fatty acids and immunity. *Adv Lipid Res* 1978;16:127-65.
10. Maple C, McLaren M, Ho M, Belch JF. Dietary supplementation with omega 3 and omega 6 fatty acids reduces whole blood white blood cell aggregation in healthy volunteers. *Prostaglandins Leukot Essent Fatty Acids* 1998;58:365-8.
11. Belch JF, Shaw B, O'Dowd A, Curran L, Forbes CD, Sturrock RD. Evening primrose oil (Efamol) as a treatment of cold-induced vasospasm (Raynaud's phenomenon). *Prog Lipid Res* 1986;25:335-40.
12. Belch JF, Ansell D, Madhok R, O'Dowd A, Sturrock RD. Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. *Ann Rheum Dis* 1988;47:96-104.
13. Veale DJ, Torley H, Richards IM, et al. A double-blind placebo controlled trial of Efamol Marine on skin and joint symptoms of psoriatic arthritis. *Br J Rheumatol* 1994;33:954-8.
14. Kremer JM. n-3 Fatty acid supplements in rheumatoid arthritis. *Am J Clin Nutr* 2000;71(suppl):349S-51S.
15. Horrobin DF. Interactions between n-3 and n-6 essential fatty acids (EFAs) in the regulation of cardiovascular disorders and inflammation. *Prostaglandins Leukot Essent Fatty Acids* 1991;44:127-31.
16. Belch JF. The role of eicosanoids in inflammation. In: Goodacre J, Dick WC, eds. *Immunopathogenic mechanisms of arthritis*. Lancaster, United Kingdom: MTP Press Ltd, 1988:26-50.
17. Belch JF. Temperature related disorders. In: Tooke J, Lowe GDO, eds. *Textbook of vascular medicine*. London: Edward Arnold, 1995:329-52.
18. Belch JF, McLaren M, Anderson J, et al. Increased prostacyclin metabolites and decreased red cell deformability in patients with systemic sclerosis and Raynaud's syndrome. *Prostaglandins Leukot Med* 1985;17:1-9.
19. Lau C, O'Dowd A, Belch JF. White cell activation in the Raynaud's phenomenon of systemic sclerosis and vibration induced white finger syndrome. *Ann Rheum Dis* 1992;51:249-52.
20. Lau CS, McLaren M, MacKay IR, Belch JF. Baseline plasma fibrinolysis and its correlation with clinical manifestations in patients with Raynaud's phenomenon. *Ann Rheum Dis* 1993;52:443-8.
21. Ralph A, Digiacomio MD, Joel M, Kremer MD, Dhiraj M, Shah MD. Fish-oil dietary supplementation in patients with Raynaud's phenomenon: a double-blind, controlled, prospective study. *Am J Med* 1989;86:158-64.
22. Tziouzas AG, Moutsopoulos HM. Sjögren's syndrome. In: Belch JF, Zurier RB, eds. *Connective tissue diseases*. London: Chapman & Hall Medical, 1995:103-30.
23. Horrobin DF. Essential fatty acid metabolism in diseases of connective tissue with special reference to scleroderma and to Sjögren's syndrome. *Med Hypotheses* 1984;14:233-47.
24. Manthorpe R, Hagen Petersen S, Prause JU. Primary Sjögren's syndrome treated with Efamol/Efavit. *Rheumatol Int* 1984;4:165-7.
25. Oxholm P, Manthorpe R, Prause JU, Horrobin D. Patients with primary Sjögren's syndrome treated for two months with evening primrose oil. *Scand J Rheumatol* 1986;15:103-8.
26. Brittner SB, Tucker WFG, Cartwright I, Bleeheh SS. A double-blind, randomised, placebo-controlled trial of fish oil in psoriasis. *Lancet* 1988;1:378-80.
27. Ziboh VA, Cohen KA, Charles EN, et al. Effects of dietary supplementation of fish oil on neutrophil and epidermal fatty acids. Modulation of clinical course of psoriatic subjects. *Arch Dermatol* 1986;122:1277-81.
28. Zurier RB, Rossetti RG, Jacobson EW, et al. Gammalinolenic acid treatment of rheumatoid arthritis: a randomized, placebo-controlled trial. *Arthritis Rheum* 1996;39:1808-17.
29. Brown J, Sim AK, De Ceular K, McLeod M, El-Ghobarey AF, Dick WC. Naudicelle in patients with rheumatoid arthritis. *Therapeutique* 1980;50:355-7.
30. Hansen TM, Lerche A, Kassis V, Lorenzen I, Sondergaard J. Treatment of rheumatoid arthritis with prostaglandin E<sub>1</sub> precursors *cis*-linoleic acid and gamma-linolenic acid. *Scand J Rheumatol* 1983;12:85-8.
31. Brzeski M, Madhok R, Capell HA. Evening primrose oil in patients with rheumatoid arthritis and side-effects of non-steroidal anti-inflammatory drugs. *Br J Rheumatol* 1991;30:370-2.
32. Lau CS, Morley KD, Belch JF. Effects of Maxepa fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis. *Br J Rheumatol* 1993;32:982-9.
33. Endres S, De Caterina R, Schmidt EB, Kristensen SD. n-3 Polyunsaturated fatty acids: update 1995. *Eur J Clin Invest* 1995;25:629-38.
34. M Hauben. Comment: evening primrose oil in the treatment of rheumatoid arthritis—proper application of statistical analysis. *Ann Pharmacother* 1993;27:1475-7.
35. Joe LA, Hart LL. Evening primrose oil in rheumatoid arthritis. *Ann Pharmacother* 1994;28:973.