Dietary Fish Oil Reduces Basal and Ultraviolet B–Generated PGE_2 Levels in Skin and Increases the Threshold to Provocation of Polymorphic Light Eruption

Lesley E. Rhodes, Brian H. Durham,* William D. Fraser,* and Peter S. Friedmann

Dermatology Unit, Department of Medicine, and *Department of Clinical Chemistry, University of Liverpool, Liverpool, United Kingdom

The sunburn response is markedly reduced by dietary fish oil rich in ω-3 polyunsaturated fatty acids. Because prostaglandins mediate the vasodilatation, we examined the effect of fish oil on ultraviolet (UV) B–induced prostaglandin metabolism. In addition we assessed the potential photoprotective effect of fish oil in light-sensitive patients.

Thirteen patients with polymorphic light eruption received dietary supplements of fish oil rich in ω-3 polyunsaturated fatty acids for 3 months. At baseline and 3 months, the minimal erythema dose of UVB irradiation was determined, and a graded UVA challenge given to a forearm to assess the threshold dose for papule provocation. Suction blisters were raised on the other forearm, on control skin, and on skin irradiated with four times the minimal erythema dose of UVB 24 h previously, and blister fluid prostaglandin E_2 was measured by radioimmunoassay. Following 3 months of fish oil, the mean minimal erythema dose of UVB irradiation increased from 19.8 ± 2.6 to 33.8 ± 3.7 mJ/cm² (mean ± SEM), $p < 0.01$. The UVA provocation test was positive in 10 patients at baseline, and after 3 months nine of these showed reduced sensitivity to papule provocation, $p < 0.001$. Before fish oil, PGE_2 increased from 8.6 (SEM 2.1) ng/ml in control skin to 27.2 (11) ng/ml after UVB, $p < 0.01$. Following 3 months of fish oil, PGE_2 decreased to 4.1 (1) and 9.6 (2.4) ng/ml in control and irradiated skin, respectively, $p < 0.05$.

Reduction of UV-induced inflammation by fish oil may be due, at least partially, to lowered prostaglandin E_2 levels. The photoprotection against UVA-provocation of a papular response suggests a clinical application for fish oil in polymorphic light eruption.
Key words: ω-3 PUFAs/photoprotection/photosensitivity disorders/photocarcinogenesis. J Invest Dermatol 105:532–535, 1995

Fish oils rich in ω-3 polyunsaturated fatty acids (PUFAs) are reported to improve a number of inflammatory disorders, including rheumatoid arthritis [1] and psoriasis [2]. They inhibit photocarcinogenesis in mice [3], and we recently reported a pronounced reduction in erythemal sensitivity to ultraviolet (UV) B in humans taking fish oil for 6 months [4].

Evidence for a role of prostaglandins in the mediation of the UVB erythemal response is provided by several studies. Intradermal injection of prostaglandin (PG) E_2 produced a prolonged erythema in humans [5]. UVB irradiation caused a fourfold increase in activity of phospholipase A_2 in guinea pig skin (Ziboh VA, Lord JT, Uematsu S, Blick G: *J Invest Dermatol* 70:211, 1978, abstract) and increased the release of eicosanoid precursor fatty acids from the phospholipids of cultured keratinocytes [6]. Suction blister PGE_2 and $PGF_{2\alpha}$ were elevated at 24 h post UVB irradiation [7,8], and indomethacin orally or topically prevented the rise in prostaglandins and partially reduced the erythemal response [9].

The anti-inflammatory effects of ω-3 PUFAs are reported to be due to their competition with ω-6 PUFAs, principally arachidonic acid, as substrates for the cyclooxygenase component of PGH_2 synthase, leading to the formation of less active prostanoids [10]. Omega-3 PUFAs, principally eicosapentaenoic acid and docosahexaenoic acid, are found in oily fish such as sardines and herrings, and hence are present in only very small amounts in the average Western diet. Dietary supplementation with ω-3 PUFAs leads to their tissue incorporation, with a pronounced increase in the ratio of ω-3 to ω-6 PUFAs in epidermal phospholipids [2,4]. A study of hairless mice showed that those fed diets high in ω-3 PUFAs had skin PGE_2 levels 2.5-fold lower than those fed diets high in ω-6 PUFAs [11], but in humans, plasma PGE_2 levels were unaffected by 4 weeks dietary fish oil [12].

Since fish oil greatly reduces the erythemal response to UVB, it is conceivable that it may confer protection against other effects of ultraviolet. We have explored this important possibility by examining the potential photoprotective effect of fish oil in polymorphic light eruption (PLE). This common and troublesome ultraviolet-induced inflammatory dermatosis can be provoked by both UVA and UVB wavebands [13], but the mechanism of the disorder is

Manuscript received March 16, 1995; final revision received June 17, 1995; accepted for publication July 6, 1995.

Reprint requests to: Dr. Lesley E. Rhodes, Dermatology Unit, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, UK.

Abbreviations: EPA, eicosapentaenoic acid; DCHA, docosahexaenoic acid; PLE, polymorphic light eruption.

0022-202X/95/$09.50 • SSDI0022-202X(95)00333-G •

unknown. The pruritic rash occurs mainly on sun-exposed sites and may comprise papules, vesicles, and plaques. Most of the currently available treatments are largely ineffective [14] and hence management of PLE mainly consists of sun-avoidance.

The present study aimed firstly to elucidate the mechanism of the reduced erythemal response to ultraviolet radiation (UVR) in humans on dietary fish oil, by examining the effect on basal and UVB-induced PGE_2 and $F_{2\alpha}$ levels in suction blister fluid. Secondly, the potential photoprotective effect on UVA provocation of lesions of PLE was assessed, to see whether fish oil might have a clinical application in this light-sensitivity disorder.

MATERIALS AND METHODS

Subjects and Study Design The Royal Liverpool University Hospital Ethics Committee approved the study, and each subject gave written informed consent. Thirteen Caucasian subjects with moderate/severe PLE (11 female, two male; median age 45 years, range 21 to 81 years) were studied during the winter months. PLE was diagnosed on the classic clinical features of a recurrent papular eruption occurring between spring and late summer, and precipitated by sun exposure. None had received phototherapy or photochemotherapy in the preceding 6 months, or were receiving systemic treatment. All continued with their usual diets during the study.

In this open study, fish oil was taken as MaxEPA (Seven Seas Ltd., Marfleet, UK), five capsules twice daily. Each capsule contains 1 g of oil, comprising 18% eicosapentaenoic acid (C20:5) and 12% docosahexaenoic acid (C22:6), both ω-3 fatty acids, the remainder comprising saturated or monosaturated fatty acids (C16:0, C16:1, C18:1).

Phototesting was performed and suction blisters induced on all PLE patients at baseline and after 3 months of fish oil. To see whether PG levels were the same in normal and PLE subjects, suction blisters were also induced at baseline in a group of 11 normal volunteers (median age 33 years, age range 24–42 years, four female) who did not take fish oil.

UVB Erythemal Sensitivity Erythemal sensitivity to broadband UVB was determined using a Philips TL12/20W fluorescent test lamp (emission spectrum 270–400 nm, peak 310 nm). The lamp was housed in a black plastic tube with five apertures of 1-cm diameter in the side. Four of the apertures were covered by neutral density filters, giving relative irradiances at the five apertures of 1.0, 0.75, 0.61, 0.51, and 0.35. A geometric series of 10 doses ranging from 7 to 80 mJ/cm^2 of erythemally weighted UVR was given in a horizontal row across the lower back, by applying the lamp directly to the skin [15]. The minimal erythema dose (MED), defined as the lowest UVR dose that produced a perceptible erythema, was assessed at 24 h.

UVA Provocation Test The apparatus used was a specially constructed "UVA arm-box" (Medical Engineering Department, Carlisle Hospitals Inc., Cumbria) comprising 15 Philips Cleo R-UVA 100-W fluorescent lamps mounted in a cylindrical arrangement, with a central irradiance of 26 mW/cm^2. The emission spectrum of the lamps was 313–370 nm, peaking at 362 nm; 0.7% of the UVR was less than 315 nm. During the provocation test, the subject's forearm was placed in the center of the box, thus exposing the whole circumference, and was supported by a handle at the closed end of the box. The forearm was marked into thirds, and a graded UVA dose was then administered by altering the time of exposure, i.e., 10 J/cm^2 to the upper forearm, 15 J/cm^2 to the mid-forearm, and 20 J/cm^2 to the lower forearm and hand. The arm was examined at 24 h for a papular reaction and the response graded as follows: 0, negative to all doses; 1, positive to 20 J/cm^2 only; 2, positive reaction to 15 J/cm^2 and above; 3, positive reaction to all doses, with mild reaction to 10 J/cm^2; and 4, positive reaction to all doses, with pronounced reaction to 10 J/cm^2.

Blister Fluid Prostaglandins Suction blisters were induced on the forearm that was not used in the provocation test. A 3-cm^2 patch on the ventral forearm was irradiated with four times the MED of UVB (mJ/cm^2) using a bank of four Philips TL12/20W fluorescent lamps. The total UV irradiance at the skin surface, at a distance of 30 cm from the lamps, was 1.25 mW/cm^2. At 24 h following irradiation, suction blisters were induced on control and irradiated skin, using two perspex suction cups, each containing a dome-shaped diaphragm with five holes 6 mm in diameter (Medical Physics Department, Royal Liverpool University Hospital, Liverpool, UK). Continuous suction at 250 mmHg below atmospheric produced bullae due to separation of dermis and epidermis [16]. Approximately 250 μl fluid was aspirated from the blisters of each cup.

Blister fluid PGE_2 and $PGF_{2\alpha}$ were measured according to the manufacturer's instructions using commercial kits (Amersham International PLC, Amersham, UK). The PGE_2 assay involves methyl oximation of the sample prior to estimation in a radioimmunoassay (RIA) that utilizes (^{125}I) PGE_2 proline-tyrosine conjugate as tracer. This assay has a sensitivity of 0.1 ng/ml and a coefficient of variation less than 10% over the range 1.25–80 ng/ml. Prostaglandin $F_{2\alpha}$ assay is an RIA that uses (^3H) $PGF_{2\alpha}$ as tracer. This assay has a sensitivity of 0.9 ng/ml and a coefficient of variation less than 10% over the range 2.4–45.0 ng/ml. Both PGE_2 and $PGF_{2\alpha}$ were found to be stable in suction blister fluid for up to 2 months when stored at −70°C. All samples were measured within 3 weeks of collection.

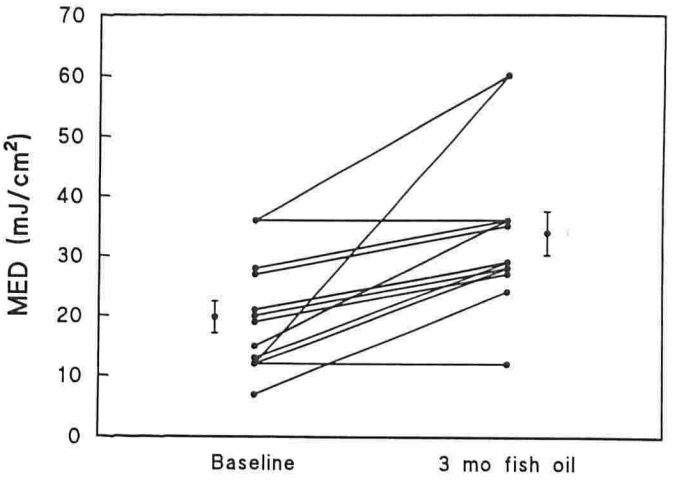

Figure 1. Dietary fish oil increases the MED of UVB. The MED of UVB (mJ/cm^2) was determined in 13 subjects with PLE at baseline and after 3 months of dietary supplementation with fish oil rich in ω-3 PUFAs. The MED, defined as the lowest UVR dose that produced a perceptible erythema, was assessed 24 h post-irradiation. Results (*bars*) are expressed as mean (SEM). The MED increased significantly, $p < 0.01$.

Statistical Methods Results concerning erythemal sensitivity to UVB irradiation and prostaglandin levels were analyzed by Student paired t test, and are presented as mean (SEM). Data from UVA challenges were analyzed by Wilcoxon's paired ranked sum test, and are presented as median (interquartile range).

RESULTS

The MED of UVB Increases Following Dietary Fish Oil Supplementation The mean MED of UVB was 19.8 ± 2.6 mJ/cm^2 at baseline, increasing to 33.8 ± 3.7 mJ/cm^2 (mean ± SEM) after 3 months fish oil, $p < 0.01$ **(Fig 1)**.

The Threshold for Provocation of PLE by UVA Increases on Dietary Fish Oil At baseline, the provocation test was positive in 10 of the 13 subjects **(Table I)**. Following 3 months of fish oil supplementation, there was evidence of reduced sensitivity to lesion provocation in nine of these 10 subjects **(Table I)**. Seven patients showed an increased threshold for provocation of lesions, and two had a mild response at 10 J/cm^2 when previously they had shown a severe reaction. The median provocation score decreased from 2 (interquartile range 0.5–3) to 0 (0–2.5) on fish oil, $p < 0.001$.

Blister Fluid PGE_2 Levels in Control and UVB-Irradiated Skin Fall During Fish Oil Therapy No significant difference was seen between the prostaglandin levels in the study (PLE) subjects before fish oil therapy and those of the normal subjects. The results in the treated group were as follows.

PGE_2: At baseline, PGE_2 increased from a mean of 8.6 ± 2.1 ng/ml in unirradiated control skin to 27.2 ± 11 ng/ml (mean ± SEM) at 24 h post-irradiation, $p < 0.01$ **(Fig 2)**. The PGE_2 levels in both unirradiated and irradiated skin fell following fish oil therapy, $p < 0.05$. After 3 months of fish oil, the PGE_2 in unirradiated skin was 4.1 ± 1 ng/ml, rising to 9.6 ± 2.4 ng/ml at 24 h post-irradiation, $p < 0.05$.

Table I. Dietary Fish Oil Supplementation Increases the Provocation Threshold of Polymorphic Light Eruption[a]

Subject	UVA Provocation Score[b] at Baseline	UVA Provocation Score[b] after 3 months of Fish Oil
1	4	3
2	4	3
3	3	2
4	3	2
5	3	2
6	3	3
7	2	0
8	1	0
9	1	0
10	1	0
11	0	0
12	0	0
13	0	0
Mean (SD)	1.92 (1.5)	1.15 (1.3)

[a] The provocation challenge was performed by irradiating three sections of the forearm with 10, 15, and 20 J/cm^2 of UVA, respectively, as described in *Materials and Methods*. The reaction was assessed at 24 h and a positive result was defined by the presence of a papular response.

[b] The papular reaction to the UVA challenge was scored as follows: 0, negative to all doses; 1, positive to 20 J/cm^2 only; 2, positive reaction to 15 J/cm^2 and above; 3, positive reaction to all doses, with mild reaction to 10 J/cm^2; and 4, positive reaction to all doses, with pronounced reaction to 10 J/cm^2.

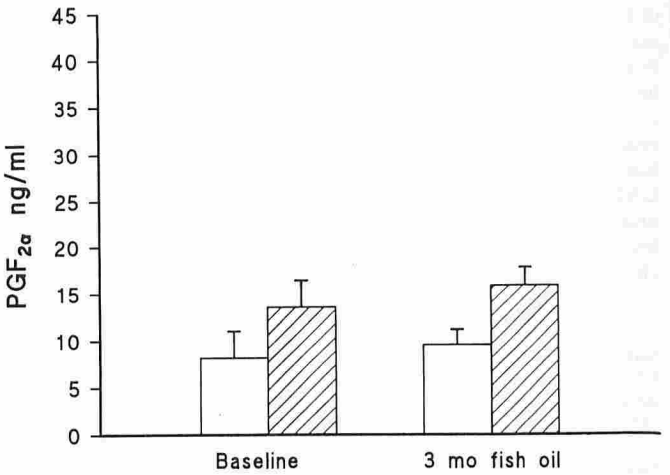

Figure 3. Dietary fish oil does not alter basal or UVB-generated levels of $PGF_{2\alpha}$ in suction blister fluid. $PGF_{2\alpha}$ levels (ng/ml) were measured in suction blister fluid obtained from control (*open bar*) and UVB-irradiated (*striped bar*) skin, at baseline and following 3 months of fish oil. Levels were measured by RIA, as described in *Materials and Methods*. n = 13, results are mean (SEM).

$PGF_{2\alpha}$: At baseline, $PGF_{2\alpha}$ increased from a mean of 8.1 ± 2.9 ng/ml in unirradiated control skin to 13.5 ± 2.9 ng/ml at 24 h following UVB, $p < 0.05$ **(Fig 3)**. In contrast to the PGE_2 findings, no significant change was seen between these baseline levels and those obtained after 3 months of fish oil.

DISCUSSION

We have shown that the reduced responsiveness to UVB-induced erythema that occurs with long-term dietary fish oil is associated with pronounced inhibition of UVB-induced PGE_2 levels in the skin. There was also a reduction in the basal PGE_2 levels. These findings suggest that the anti-inflammatory effects of ω-3 PUFAs in humans are at least partially due to reduction of prostaglandin synthesis. $PGF_{2\alpha}$ levels were not reduced on fish oil, but when injected intradermally this mediator is much less potent than PGE_2 in the production of cutaneous erythema [5]. Reduced sensitivity to UV provocation of rash in our light-sensitive patients shows that the protective effect of dietary fish oil extends from the sunburn response to an inflammatory disease process, suggesting a clinical application for this novel and safe [17] systemic photoprotective agent.

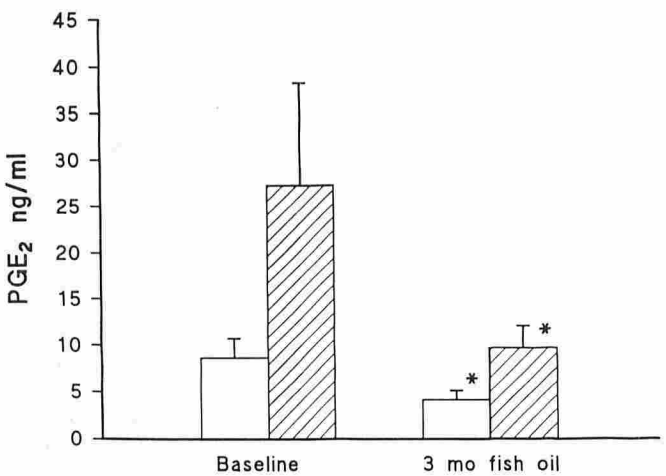

Figure 2. Dietary fish oil reduces basal and UVB-generated levels of PGE_2 in suction blister fluid. PGE_2 levels (ng/ml) were measured in suction blister fluid obtained from control (*open bar*) and UVB-irradiated (*striped bar*) skin, at baseline and following 3 months of fish oil. Levels were measured by RIA, as described in *Materials and Methods*. n = 13, results are mean (SEM). *$p < 0.05$ compared to corresponding levels before dietary supplementation.

Reduction of PGE_2 levels on dietary fish oil could be due to interference with prostaglandin synthesis at more than one step by ω-3 PUFAs. ω-3 PUFAs compete with ω-6 PUFAs for metabolism by cyclooxygenase, leading to the production of less active prostaglandins [10]. In addition, the high proportion of ω-3 PUFAs in the epidermal phospholipids on dietary fish oil [4], together with their more ready release than ω-6 PUFAs following UV irradiation [6], suggests that they may compete with the ω-6 PUFAs for release from cell membranes by phospholipases. The lack of a reduction in $PGF_{2\alpha}$ levels also suggests that fish oil selectively inhibits PGE synthase but not PGF isomerase. Other mechanisms that may be involved in the anti-inflammatory action of ω-3 PUFAs are reduced synthesis of leukotrienes [18] and of the cytokines interleukin-1 and tumor necrosis factor-α [19]. Previous studies by ourselves and other investigators [4,20] suggest that the unstable ω-3 PUFAs in fish oil also act as an oxidizable buffer. They appear to be preferentially damaged by free radicals, thus protecting more essential structures from free-radical damage. This mechanism for the anti-inflammatory effect of ω-3 PUFAs could also result in reduced availability of free radicals for prostaglandin generation.

Current evidence suggests an immunologic basis for PLE, i.e., a delayed hypersensitivity response [21], but it is conceivable that PGs are involved in the inflammation. Mepacrine, a toxic but useful anti-inflammatory treatment in PLE, may act by reducing PG synthesis [22], probably by inhibition of phospholipase A_2 activity [23]. Nine of our study subjects had taken a course of fish oil therapy through a previous spring and summer (unpublished data). All reported some clinical benefit, the patients estimating an average of 50% (range 10–100%) improvement in their rash, and three subjects experienced no rash at all for the first summer since their disorder started. The currently available treatments for PLE are either ineffective, such as β-carotene [24]; have serious side effects, such as systemic steroids or the anti-malarials [25]; or involve repeated visits to the hospital, e.g., PUVA therapy [26].

Our findings may therefore signify a considerable advance in the treatment of PLE.

Hence we now have evidence that dietary fish oil protects against UV provocation of a photosensitivity disorder as well as the sunburn response, and that some of the photoprotective properties may be mediated, at least partly, by reduced PGE_2 levels. A formal therapeutic trial of fish oil therapy in PLE is now indicated. Finally, because there is evidence that PGE_2 may have a role in the growth of cutaneous carcinomas [27], and that diets rich in ω-3 PUFAs inhibit UV-induced cutaneous carcinomas in animals [3], long-term studies are also warranted to examine the effect of fish oil on photocarcinogenesis in humans.

We are grateful to Professor Malcolm J. Jackson for his critical reading of the manuscript.

REFERENCES

1. Kremer JM, Jubiz W, Michalek A, Rynes RI, Bartholomew LE, Bigaouette J, Timchalk M, Beeler D, Lininger L: Fish-oil fatty acid supplementation in active rheumatoid arthritis. *Ann Intern Med* 106:497–503, 1987
2. Ziboh VA, Cohen KA, Ellis CN, Miller C, Hamilton TA, Kragballe K, Hydrick CR, Vorhees JJ: Effects of dietary supplementation of fish oil on neutrophil and epidermal fatty acids. *Arch Dermatol* 122:1277–1282, 1986
3. Orengo I, Black HS, Kettler AH, Wolf JE: Influence of dietary menhaden oil upon carcinogenesis and various cutaneous responses to ultraviolet radiation. *Photochem Photobiol* 49:71–77, 1989
4. Rhodes LE, O'Farrell S, Jackson MJ, Friedmann PS: Dietary fish-oil supplementation in humans reduces UVB-erythemal sensitivity but increases epidermal lipid peroxidation. *J Invest Dermatol* 103:151–154, 1994
5. Crunkhorn P, Willis AL: Cutaneous reactions to intradermal prostaglandins. *Br J Pharmac* 41:49–56, 1971
6. Punnonen K, Puustinen T, Jansen CT: Ultraviolet B irradiation induces changes in the distribution and release of arachidonic acid, dihomo-δ-linolenic acid, and eicosapentaenoic acid in human keratinocytes in culture. *J Invest Dermatol* 88:611–614, 1987
7. Black AK, Greaves MW, Hensby CN, Plummer NA: Increased prostaglandins E_2 and $F_{2\alpha}$ in human skin at 6 and 24 H after ultraviolet B irradiation (290–320 nm). *Br J Clin Pharmac* 5:431–436, 1978
8. Gilchrest BA, Soter NA, Stoff JS, Mihm MC: The human sunburn reaction: histologic and biochemical studies. *J Am Acad Dermatol* 5:411–422, 1981
9. Black AK, Greaves MW, Hensby CN, Plummer NA, Warin AP: The effects of indomethacin on arachidonic acid and prostaglandins E_2 and $F_{2\alpha}$ levels in human skin 24 H after UVB and UVC irradiation. *Br J Clin Pharmac* 6:261–266, 1978
10. Lands WEM. Biochemistry and physiology of n-3 fatty acids. *FASEB J* 6:2530–2536, 1992
11. Henderson CD, Black HS, Wolf JE: Influence of omega-3 and omega-6 fatty acid sources on prostaglandin levels in mice. *Lipids* 24:502–505, 1989
12. Orengo IF, Black HS, Wolf JE: Influence of fish oil supplementation on the minimal erythema dose in humans. *Arch Dermatol Res* 284:219–221, 1992
13. Frain-Bell W, Dickson A, Herd J, Sturrock I: The action spectrum in polymorphic light eruption. *Br J Dermatol* 89:243–249, 1973
14. Corbett MF, Hawk JLM, Herxheimer A, Magnus IA: Controlled therapeutic trials in polymorphic light eruption. *Br J Dermatol* 107:571–581, 1982
15. Diffey BL, Oliver RJ: An inexpensive luminaire for diagnostic testing to UVB radiation. *Photodermatology* 2:260–262, 1985
16. Kiistala U: Suction blister device for separation of viable epidermis from dermis. *J Invest Dermatol* 50:129–137, 1968
17. Saynor R, Gillott T: Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. *Lipids* 27:533–538, 1992
18. Lee TH, Hoover RL, Williams JD, Sperling RI, Ravalese J, Spur BW, Robinson DR, Corey EJ, Lewis RA, Austen KF: Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. *N Engl J Med* 312:1217–1224, 1985
19. Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, van der Meer JWM, Cannon JG, Rogers TS, Klempner MS, Weber PC, Schaefer EJ, Wolff SM, Dinarello CA: The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumour necrosis factor by mononuclear cells. *N Engl J Med* 320:265–271, 1989
20. van den Berg JJM, de Fouw NJ, Kuypers FA, Roelofsen B, Houtsmuller UMT, Op den Kamp JAF: Increased n-3 polyunsaturated fatty acid content of red blood cells from fish oil-fed rabbits increases in vitro lipid peroxidation, but decreases haemolysis. *Free Rad Biol Med* 11:393–399, 1991
21. Norris PG, Barker JNWN, Allen MH, Leiferman KM, MacDonald DM, Haskard DO, Hawk JLM: Adhesion molecule expression in polymorphic light eruption. *J Invest Dermatol* 99:504–508, 1992
22. Greaves MW, McDonald-Gibson WJ: Anti-inflammatory agents and prostaglandin biosynthesis (letter). *Br Med J* 3:527, 1972
23. Vargaftig BB, Hai ND: Selective inhibition by mepacrine of the release of "rabbit aorta contracting substance" evoked by the administration of bradykinin. *J Pharmac Pharmacol* 24:159–161, 1972
24. Mathews-Roth MM, Pathak MA, Fitzpatrick TB, Harber LC, Kass EH: Beta-carotene therapy for erythropoietic protoporphyria and other photosensitivity disorders. *Arch Dermatol* 113:1229–1232, 1973
25. Epstein JH: Polymorphous light eruption. *J Am Acad Dermatol* 3:329–343, 1980
26. Parrish JA, Le Vine MJ, Morison WL, Gonzalez E, Fitzpatrick TB: Comparison of PUVA and beta-carotene in the treatment of polymorphous light eruption. *Br J Dermatol* 100:187–191, 1979
27. Vanderveen EE, Grekin RC, Swanson NA, Kragballe K: Arachidonic acid metabolites in cutaneous carcinomas. *Arch Dermatol* 122:407–412, 1986