

n-3 Fatty acids in psoriasis

P. Mayser^{1*}, H. Grimm² and F. Grimminger³

¹Department of Dermatology and Andrology, ²The Department of General and Thoracic Surgery, Justus Liebig University, Giessen, Gaffkystr. 14, D-35385 Giessen, Germany

³Department of Internal Medicine, Justus Liebig University, D-35385 Giessen, Germany

Increased concentrations of free arachidonic acid (AA) and its proinflammatory metabolites have been observed in psoriatic lesions. Replacement of arachidonic acid by alternative precursor polyunsaturated fatty acids (PUFA), especially eicosapentaenoic acid (EPA), which can be metabolized via the same enzymatic pathways as AA, might be a therapeutic option in psoriasis. However the results of studies evaluating the therapeutic benefit of dietary fish oil have been conflicting and not clearly dose-dependent. To overcome the slow kinetics and limited availability of oral supplementation, we have performed three studies to assess the efficacy and safety of an intravenously administered fish oil derived lipid emulsion on different forms of psoriasis. Patients received daily infusions of either an *n*-3 fatty acid-based lipid emulsion (Omegaven[®]) or a conventional *n*-6 lipid emulsion (Lipoven[®]) in different time and dose regimens. In addition to an overall assessment of the clinical course of psoriasis, EPA- and AA-derived neutrophil 5-lipoxygenase (LO)—products, thromboxane (TX) B₂/B₃, PAF and plasma free fatty acids were investigated. Treatment with *n*-3 fatty acids resulted in a considerably higher response rate than infusion of *n*-6 lipids. A more than 10-fold increase in neutrophil EPA-derived 5-LO product formation was noted in the *n*-3 group, accompanied by a rapid increase in plasma-free EPA within the first days. In conclusion, intravenous *n*-3-fatty acid administration causes reduction of psoriasis, which may be related to changes in inflammatory eicosanoid generation. The rapidity of the response to intravenous *n*-3 lipids exceeds by orders of magnitude the hitherto reported kinetics of improvement of psoriatic lesions upon use of oral supplementation.

n-3 Fatty acids: Fish oil: Psoriasis: Inflammation: Eicosanoids

Introduction

Psoriasis is a common inflammatory skin disorder, affecting 2% of the population in western countries. It is characterized by pronounced hyperproliferation of keratinocytes, combined with markedly increased vascularization of the skin, fibroblast activation and *leucocyte* infiltration (Christophers & Sterry, 1993). The pathogenesis has not been entirely clarified (Christophers, 1996). The role of infiltrating white blood cells in initiating psoriasis has stimulated a search for chemotactic and proinflammatory factors, of which cytokines and lipid mediators have emerged as principal protagonists. As part of a multifactorial process, profound changes in the metabolism of eicosanoids with increased concentrations of free arachidonic acid and its pro-inflammatory metabolites (leukotriene B₄—LTB₄, hydroxyeicosatetraenoic acids—HETE) have been observed in psoriatic lesions (Christophers &

Sterry, 1993; Grimminger & Mayser, 1995). These metabolites have a chemotactic effect on skin-infiltrating *leucocytes*, in particular on neutrophils, and may enhance keratinocyte proliferation.

Release of free arachidonic acid from membrane phospholipid pools is the rate-limiting step in eicosanoid synthesis. LTB₄ generated by the neutrophil can stimulate the cell in an autocrine way (Mahadevappa & Powell, 1989; Grimminger *et al.* 1992). Interestingly, keratinocytes can cooperate in leukotriene synthesis. Intermediate LTA₄ secreted by the neutrophil can be further metabolized by adjacent keratinocytes (Sola *et al.* 1992; Iversen *et al.* 1993). The resulting chemotactic gradient may direct the activated neutrophil from the microvessel towards the subcorneal microabscesses in psoriatic skin lesions.

Therefore, replacement of arachidonic acid by alternative precursor polyunsaturated fatty acids (PUFA), especially eicosapentaenoic acid (EPA), might be a therapeutic

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFA, free fatty acids; HETE, hydroxyeicosatetraenoic acid; LTB₄, leukotriene B₄; LTB₅, leukotriene B₅; PASI, psoriasis area and severity index; PMN, polymorphonuclear leucocyte; PUFA, polyunsaturated fatty acid; T_h, T-helper cell; T_x, thromboxane.

* **Corresponding author:** PD Dr P. Mayser, email Peter.Mayser@derma.med.uni-giessen.de

starting point in psoriasis. EPA, the *n*-3 pentaene analogue of AA, can be metabolized via the same enzymatic pathways as AA (Goldman *et al.* 1983; Lee *et al.* 1984; Heidel *et al.* 1989). However, the chemotactic and neutrophil-activating capacity of LTB₅ derived from EPA is more than ten times lower than that of LTB₄ and it is a less potent stimulator of keratinocyte proliferation (Kragballe *et al.* 1987).

A number of studies have evaluated the therapeutic benefit of *n*-3 fatty acids in psoriasis, either using fish oil or highly purified *n*-3 fatty acid ethyl esters. However, despite the fact that sometimes high amounts of *n*-3 fatty acids are ingested by the patients, the results have been conflicting and not clearly dose-dependent (Grimminger & Mayser, 1995; Table 1). Therefore, we conducted three studies addressing acute-exanthematic and chronic-plaque type manifestations of psoriasis with extended skin involvement in hospitalized patients with intravenous application of EPA (Grimminger *et al.* 1993a; Mayser *et al.* 1996, 1998). The intravenous route was chosen to guarantee rapid availability of *n*-3 fatty acids and to provide increased plasma levels of EPA in non-esterified form. Free EPA can directly compete with AA at the level of intracellular eicosanoid synthesis and so can potentially exert a rapid and profound effect on inflammatory activity in psoriatic lesions (Grimminger *et al.* 1992).

Description of the studies

All trials were conducted with identical lipid emulsions (Omegaven or Lipoven) obtained from Fresenius AG, Oberursel, FRG. Their composition is shown in Table 2.

In the first double-blind, parallel-group, placebo-controlled study conducted in 1990–1, 20 patients with acute-exanthematic psoriasis were randomly allocated to receive twice daily infusions of 50 ml *n*-3 fatty acid-based lipid emulsion (Omegaven) or conventional *n*-6-lipid emulsion (Lipoven) for 10 days (Grimminger *et al.* 1993a). In addition to clinical parameters (erythema,

infiltration, desquamation, subjective score) neutrophil 4-*v.* 5-series leukotriene generation was investigated. During the trial period additional psoriasis therapy was restricted to topical application of 0.03% cignolin in white petrolatum.

In a second trial, a patient with relapsing acute-exanthematic psoriasis was twice under therapy with an *n*-3 lipid emulsion (Mayser *et al.* 1996). In the first 10-day intervention, he received 50 ml Omegaven twice daily. Additional anti-psoriatic therapy was restricted to topical application of 0.03% cignolin vaseline. The severity of the disease was evaluated by the Psoriasis Area and Severity Index (PASI)-Score (Fredriksson & Petersson, 1978). One year later, the patient asked for a second intervention with Omegaven because of his previous good experience. Since the relapse was much more extended, the previous dose was doubled (2 × 100 ml) and therapy was performed for a period of 15 days. During the intervention, therapy was restricted to bland emulsifying ointment.

The third trial, a double-blind, randomized, parallel group study, was performed in eight European centers for dermatology (Mayser *et al.* 1998). Eighty-three patients hospitalized for chronic-plaque-type psoriasis with a severity of at least 15 according to PASI were randomly allocated to receive twice daily infusions with 100 ml Omegaven or Lipoven for 14 days. Efficacy of therapy was evaluated by changes in PASI, in an overall assessment of psoriasis by the investigator, and a self-assessment by the patient. In one center neutrophil 4-*v.* 5-series leukotriene (LT) generation and platelet 2-*v.* 3-thromboxane generation were investigated and plasma-free fatty acids were determined.

The details of these three trials are summarised in Table 3.

Results of the trials

In all trials *n*-3 lipid emulsion had a positive influence on the course of psoriasis. The effect seemed to be more pronounced in the inflammatory, acute-exanthematic forms of the disease. Obvious side-effects of the lipid

Table 1. Studies to evaluate the therapeutical benefit of orally applied *n*-3 fatty acids, either using fish oil or highly purified *n*-3 fatty-acid ethyl esters

Author/year	Design ^a	Route	Clinical form/cases completed	Days	Oil ^b (g/d)	EPA (g/d)	DHA (g/d)	Result ^c
Ziboh <i>et al.</i> 1986	open	oral	stable-plaque/13	56	60–75*	10.8–13.5	7.2–9.0	+
Maurice <i>et al.</i> 1987	open	oral	stable-plaque/10	42	25–50*	4.5–9.0	6.0	+
Bittiner <i>et al.</i> 1988	db. pc	oral	stable-plaque/28	56	10*	1.8	1.2	+
Bjorneboe <i>et al.</i> 1988	db. Pc	oral	stable-plaque/27	56	10*	1.8	1.2	–
Kettler <i>et al.</i> 1988	open	oral	stable-plaque/22 pustular/1	ca. 50	18*	3.2	2.2	–
Kragballe <i>et al.</i> 1989	open	oral	stable-plaque/26	120	30*	5.4	3.6	+
Kojima <i>et al.</i> 1989	open	oral	stable-plaque/9	90–180	4**	3.6		+
Schena <i>et al.</i> 1989	open	oral	stable-plaque/13	56	20***	1.3	1.7	+
Dewsbury <i>et al.</i> 1989	sb. pc	topical	stable-plaque/11	49	–*			+
Lassus <i>et al.</i> 1990	open	oral	stable-plaque/76 (34 with arthritis)	56	6**	1.1	0.8	+
Linker <i>et al.</i> 1991	db. pc	oral	stable-plaque/60	84	9*	1.6	1.0	+
Escobar <i>et al.</i> 1992	sb. pc	topical	stable-plaque/25	28	–*			+
Henneicke <i>et al.</i> 1993	db. Pc	topical	stable-plaque/52	56	–**			–
Soyland <i>et al.</i> 1993	db. pc	oral	stable-plaque/145	120	6**	3.1	1.9	–

^a db = double-blind. sb = single-blind. pc = placebo-controlled.

^b *Fish-oil preparations; **highly purified *n*-3-PUFA-ethylesters; ***cod-liver oil.

^c + = improvement; – = no effect.

Table 2. Fatty acid composition of n-3- and n-6-lipid emulsions

Fatty acid (g/l)		Omegaven	Lipoven
Myristic acid	C14:0	4.6	–
Palmitic acid	C16:0	9.0	12.4
Palmitoleic acid	C16:1n7	7.6	–
Stearic acid	C18:0	1.8	4.2
Oleic acid	C18:1n9	11.5	23.0
Linoleic acid	C18:2n6	2.8	52.9
Alpha-Linolenic acid	C18:3n3	1.7	7.6
Arachidonic acid	C20:4n6	1.5	–
Eicosapentaenoic acid	C20:5n3	21.1	–
Docosapentaenoic acid	C22:5n3	2.8	–
Docosahexaenoic acid	C22:6n3	21.5	–
Others		15.4	–

infusion regimens were restricted to rare irritations at the site of peripheral intravenous route. Fasting serum triacylglycerol concentrations decreased significantly in most patients after infusion of the n-3 emulsion, while serum cholesterol was unchanged.

Trial 1: A moderate improvement in clinical manifestations was noted in the n-6 group (changes in score systems between 16% and 25% from baseline within 10 days). In contrast, the severity of disease markedly decreased in all patients of the n-3 group, with improvement in all score systems ranging between 45% and 76% within 10 days ($P < 0.05$ for each variable). The difference in response of the two regimens was evident within 4–7 days after onset of lipid infusion. A more than 10-fold increase in neutrophil EPA-derived 5-lipoxygenase product formation (LTB₅, its omega-oxidation products, non-enzymatic degradation products of LTA₅ and 5-hydroxyeicosapentaenoic acid) was noted in the n-3 group but not in the n-6 group. This increase in EPA-derived product formation was clearly evident on day 3 (first analysis after onset of infusion), progressed continuously to day 10, and was followed by a drop to baseline values within 30 days after termination of the infusion. Neutrophil PAF generation increased in the n-6 group but decreased in the n-3 group. Partial relapse phenomena were noted in some patients within 1–2 weeks after terminating the n-3 lipid infusions.

Trial 2: During the first treatment period PASI-Score dropped from 18.4 to 4.2. In addition, leukotriene (LT) generation of ionophore-stimulated neutrophils showed a more than 10-fold increase in EPA-derived lipoxygenase product formation. Probably because of a worse clinical condition in the second treatment period, the patient

responded more slowly than during the first period (improvement of PASI from 22.2 to 8), and the increase of EPA-derived metabolites was more retarded.

Trial 3: The total PASI score decreased by 11.2 ± 9.8 in the n-3 and by 7.5 ± 8.8 in the n-6 group ($P=0.048$). In addition, the n-3 group was superior to the n-6 group with respect to change in severity of psoriasis per body area, change in overall erythema, overall scaling and overall infiltration as well as change in overall assessment by the investigator and self-assessment by the patient. Response (defined as decrease in total PASI of at least 50% between admission and last value) was seen in sixteen out of forty-three patients (37%) under n-3 and nine out of forty patients (23%) under n-6 fatty acid-based lipid emulsion. Within the first few days of n-3 lipid administration, but not in the n-6 supplemented patients, a significant increase in neutrophil LTB₅ and platelet TxB₃ generation and plasma-free EPA concentration occurred (Fig. 1a/b).

Discussion

A number of studies have evaluated the therapeutic benefit of n-3 fatty acids either using fish oil or highly purified n-3 fatty acid ethyl esters by the oral or topical route (Grimminger & Mayser, 1995). The present investigations were conducted to demonstrate the efficacy and safety of an n-3 fatty-acid-based lipid infusion in patients with acute-exanthematic and chronic plaque psoriasis. In contrast to oral n-3 fatty acid supplementation, intravenous infusion of EPA- and DHA-containing triglycerides was chosen to achieve substantial plasma levels of alternative precursor fatty acids within a short period of time.

n-3 Lipids caused a statistically significant larger decrease in the clinical symptoms of psoriasis compared with n-6 lipids, and a considerably higher response rate than infusion of n-6 lipids. In the first trial changes in score systems between 16% and 25% from baseline were noted within 10 days in the n-6 group and between 45% and 76% in the n-3 group (Grimminger *et al.* 1993a). The second trial showed that n-3 lipid infusions are successful even in relapsing psoriasis (Mayser *et al.* 1996). With response being defined as a decrease in total PASI between admission and last assessment of at least 50% in the third trial 37% were found to be responders in the n-3 lipid group and 23% in the n-6 lipid group within a 14 day-treatment period (Mayser *et al.* 1998).

Data from both double-blind studies strongly suggest that differences between the two lipid infusion groups were due

Table 3.

Year	Clinical form	No. of patients	Days	Dose g/day		Biochemical parameters determined
				EPA	DHA	
1990	Acute-exanthematic	20	10	2.1	2.1	EPA- and AA-derived 5 LO-products; PAF
1995	Acute-exanthematic	1	10	2.1	2.1	EPA- and AA-derived 5 LO-products
			15	4.2	4.2	
1996	Chronic-plaque	83	14	4.2	4.2	EPA- and AA-derived 5 LO-products; plasma FFA; TXB ₂ /B ₃

DHA = docosahexaenoic acid.

The experimental procedures for determination of neutrophil-derived 5-LO products, PAF, plasma-free fatty acids and TXB₂/B₃ are described in detail in the publications by Hjorth *et al.* 1981, Grimminger *et al.* 1988a/b, Pace-Asciak, 1989, Grimminger *et al.* 1993a/b and Krämer *et al.* 1993.

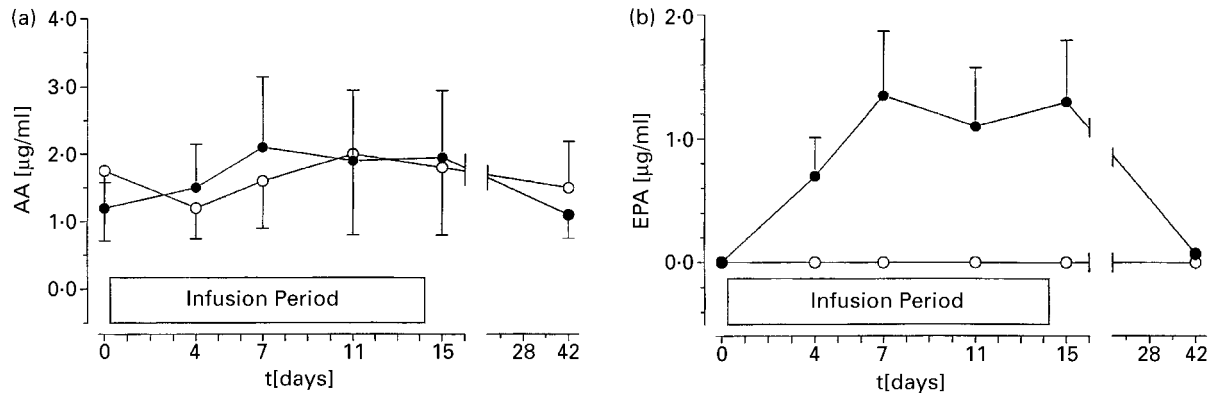


Fig. 1. Time course of plasma-free arachidonic (a) resp. eicosapentaenoic acid (b) during days 1–15, as well as 14 and 28 days after the infusion periods with *n*-6- (○) or *n*-3- (●)- lipid emulsion. Blood was collected immediately before onset of infusion. Data are given as µg/ml (mean \pm sem).

to an improvement in the *n*-3 lipid group rather than deterioration in the *n*-6 lipid group. It may even be speculated that intravenous *n*-6 fatty acid infusion caused some regression of the psoriatic lesions. Such findings might be related to the pharmacological effects of the high amount of linoleic acid in the *n*-6 lipid infusion, as previously discussed (Ruzicka & Groß, 1989). However, to support such speculation, an additional control group would be needed, which was excluded by the blinded protocol in both studies.

In all trials no severe adverse effects of the *n*-3 fatty acid-based preparation in the psoriatic patients were noted. Laboratory variables remained in the normal range, and plasma triglyceride levels even decreased, which is in line with the well-established effects of *n*-3 lipids on lipid metabolism.

As previously described (Mascioli *et al.* 1989; Von Schacky & Weber, 1985), baseline plasma levels of EPA are low. A rapid increase in plasma-free EPA within the first days of *n*-3 lipid infusion was demonstrated in the third study. This finding signals rapid hydrolysis of the esterified precursor: infusion of artificial lipid aggregates may activate endothelial lipoprotein lipase, including translocation of the enzyme from its cellular binding site into the vascular compartment (Yamazaki *et al.* 1991; Grimmering *et al.* 1992; Peterson *et al.* 1990). The increasing plasma lipolytic activity will then cause a rise in plasma-free fatty acids, which escape local cellular uptake mechanism. Thus, the kinetics and extent of plasma EPA increase observed in the third study exceed by far corresponding alterations in response to usual dietary fish oil uptake (Harris *et al.* 1988). Parallel with the plasma-free EPA increase, a rise of neutrophil LTB₅ generation and platelet TxB₃ formation occurred, indicating the influence of the alternative fatty acid precursor on the lipoxygenase and cyclooxygenase pathways. Notably, this shift to 5-series leukotrienes and 3-series Tx generation was observed upon *in vitro* challenge of neutrophils and platelets in the absence of plasma in the present study. These findings suggest that some EPA-containing membrane lipid pool(s), providing precursor fatty acids to the metabolic pathways of eicosanoid formation, may be rapidly regulated in exchange with plasma EPA. It remains speculative whether the generation

of EPA-derived metabolites might even be markedly higher upon neutrophil and platelet stimulation with natural agonists in EPA-containing environments. For example, it is known that inflammatory agents occurring in psoriatic lesions, such as LTB₄ and platelet activating factor, critically depend on the presence of extracellular precursor fatty acid for induction of LT generation and PMN activation (Grimmering *et al.* 1992; Mahadevappa & Powell, 1989). In the presence of substantial microenvironmental concentrations of free EPA, neutrophil-keratinocyte cooperation in eicosanoid biosynthesis, suggested to be responsible for the high local concentrations of eicosanoids in psoriasis (Sola *et al.* 1992; Iversen *et al.* 1993), must be assumed to be shifted to the less potent and partially antagonistic EPA-derived metabolites.

It remains questionable whether skin lesions might improve even more impressively by infusion of higher *n*-3 lipid doses than those used in our trials, which are known to provide more elevated plasma-free EPA concentrations (Grimmering *et al.* 1993b). Furthermore it would be of interest whether comparable effects could be achieved by a once daily application, which would be optimal for outpatient therapy. In summary, intravenous *n*-3 lipid supplementation could widen the treatment options in acute-exanthematic and severe chronic-plaque type psoriasis with special emphasis to rotational therapeutic procedures and to combination regimens together with topical anti-psoriatic compounds such as dithranol or vitamin D₃ analogues.

References

- Bittiner SB, Tucker WF, Cartwright I & Bleehen SS (1988) A double-blind, randomised, placebo-controlled trial of fish oil in psoriasis. *Lancet* **20**, 78–380.
- Bjorneboe A, Smith AK, Bjorneboe GE, Thune PO & Drevon CA (1988) Effect of dietary supplementation with *n*-3 fatty acids on clinical manifestations of psoriasis. *British Journal of Dermatology* **118**, 77–83.
- Christophers E & Sterry W (1993) Psoriasis. In *Dermatology in General Medicine*, pp. 489–515 [Th Fitzpatrick, AZ Eisen and K Wolff, editors]. New York, NY: McGraw Hill.
- Christophers E (1996) The immunopathology of psoriasis. *International Archives of Allergy and Immunology* **110**, 199–206.

- Dewsbury CE, Graham P & Darley CR (1989) Topical eicosapentaenoic acid (EPA) in the treatment of psoriasis. *British Journal of Dermatology* **120**, 581.
- Escobar SO, Achenbach R, Iannantuono R & Torem V (1992) Topical fish oil in psoriasis — a controlled and blind study. *Clinical and Experimental Dermatology* **17**, 159–162.
- Fredriksson T & Pettersson U (1978) Severe psoriasis — oral therapy with a new retinoid. *Dermatologica* **157**, 238–244.
- Goldman DW, Pickett WC & Goetzl EJ (1983) Human neutrophil chemotactic and degranulating activities of leucotriene B₅ (LTB₅) derived from eicosapentaenoic acid. *Biochemical and Biophysical Research Communications* **117**, 282–288.
- Grimminger F, Becker G & Seeger W (1988a) High yield enzymatic conversion of intravascular leukotriene A₄ in blood-free perfused lungs. *Journal of Immunology* **141**, 2431–2436.
- Grimminger F, Menger M, Becker G & Seeger W (1988b) Potentiation of leukotriene generation following sequestration of neutrophils in isolated lungs. *Blood* **72**, 1687–1692.
- Grimminger F, Dürr U & Seeger W (1992) Ligand-operated synthesis of 4-series and 5-series leukotrienes in human neutrophils: critical dependence on exogenous free fatty acid supply. *Molecular Pharmacology* **41**, 757–766.
- Grimminger F, Mayser P, Papavassilis C, Thomas M, Schlotzer E & Heuer KU (1993a) A double-blind, randomized, placebo-controlled trial of n-3 fatty acid-based lipid infusion in acute, extended guttate psoriasis. *Clinical Investigator* **71**, 634–643.
- Grimminger F, Führer D & Papavassilis C (1993b) Influence of intravenous n-3 lipid supplementation on fatty acid profiles and lipid mediator generation in a patient with severe ulcerative colitis. *European Journal of Clinical Investigation* **23**, 706–715.
- Grimminger F & Mayser P (1995) Lipid mediators, free fatty acids and psoriasis. A review. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **52**, 1–15.
- Harris WS, Zucker ML & Dujovne CA (1988) ω-3 Fatty acids in hypertriglyceridemic patients. Triglycerides vs methyl esters. *American Journal of Clinical Nutrition* **48**, 992–997.
- Heidel JR, Taylor SM, Laegreid WW, Silflow RM, Liggitt HD & Leid RW (1989) *In vivo* chemotaxis of bovine neutrophils induced by 5-lipoxygenase metabolites of arachidonic and eicosapentaenoic acid. *American Journal of Pathology* **134**, 671–676.
- Henneicke von Zepelin HH, Mrowietz U, Färber L, Bruck-Borchers K, Schober C, Huber J, Lutz G, Kohnen R, Christophers E & Welzel D (1993) Highly purified omega-3-polyunsaturated fatty acids for topical treatment of psoriasis. Results of a double-blind, placebo-controlled multicentre study. *British Journal of Dermatology* **129**, 713–717.
- Hjorth R, Jonsson A-K & Vretblad P (1981) A rapid method for purification of human granulocytes using Percoll. A comparison with dextran sedimentation. *Journal of Immunological Methods* **43**, 95–99.
- Iversen L, Fogh K & Ziboh VA (1993) Leukotriene B₄ formation during human neutrophil keratinocyte interactions: Evidence for the transformation of leukotriene A₄ by putative keratinocyte leukotriene A₄ hydrolase. *Journal of Investigative Dermatology* **100**, 293–298.
- Kettler AH, Baughn RE, Orengo IF, Black H & Wolf JE Jr (1988) The effect of dietary fish oil supplementation on psoriasis. Improvement in a patient with pustular psoriasis. *Journal of the American Academy of Dermatology* **18**, 1267–1273.
- Kojima T, Terano T, Tanabe E, Okamoto S, Tamura Y & Yoshida S (1984) Effect of highly purified eicosapentaenoic acid on psoriasis. *Journal of the American Academy of Dermatology* **21**, 150–151.
- Krämer HJ, Stevens J & Seeger W (1993) Analysis of 2- and 3-series prostanoids by post-HPLC ELISA. *Analytical Biochemistry* **214**, 535–543.
- Kragballe K, Vorhees JJ & Goetzl EJ (1987) Inhibition by leucotriene B₅ of leucotriene B₄ — induced activation of human keratinocytes and neutrophils. *Journal of Investigative Dermatology* **88**, 555–558.
- Kragballe K & Fogh K (1989) A low-fat diet supplemented with dietary fish oil (Max-EPA) results in improvement of psoriasis and in formation of leukotriene B₅. *Acta Dermato-Venereologica Stockh* **69**, 23–28.
- Lassus A, Dahlgren AL, Halpern MJ, Snatalahti J & Happonen HP (1990) Effects of dietary supplementation with polyunsaturated ethyl ester lipids (Angiosan) in patients with psoriasis and psoriatic arthritis. *The Journal of International Medical Research* **18**, 68–73.
- Lee TH, Mencia-Huerta JM, Shih C, Corey E, Lewis RA & Austen FK (1984) Characterization and biologic properties of 5,12-dihydroxy-derivatives of eicosapentaenoic acid, including leukotriene B₅ and the double lipoxygenase products. *Journal of Biological Chemistry* **259**, 2383–2389.
- Linker U, Ständer M & Oette K (1991) Besserung klinischer Symptome der Psoriasis durch Fischöl. *Aktuelle Dermatologie* **17**, 70–74.
- Mascioli EA, Lopes S, Randall S, Porter KA, Kater G & Hirschberg Y (1989) Serum fatty acid profiles after intravenous medium chain triglyceride administration. *Lipids* **24**, 793–798.
- Mahadevappa VG & Powell WS (1989) The metabolism of arachidonic and eicosapentaenoic acids in human neutrophils stimulated by A23187 and FMLP. *Journal of Cellular Biochemistry* **40**, 341–352.
- Maurice PD, Allen BR, Barkley AS, Cockbill SR, Stammers J & Bather PC (1987) The effects of dietary supplementation with fish oil in patients with psoriasis. *British Journal of Dermatology* **117**, 599–606.
- Mayser P, Grimminger F, Papavassilis C, Schlotzer E & Seeger W (1996) Reproducible effects of intravenously administered fish-oil in acute exacerbating psoriasis. *Journal of Dermatological Treatment* **7**, 211–214.
- Mayser P, Mrowietz U, Arenberger P, Bartak P, Buchvald J, Christophers E, Jablonska S, Salmhofer W, Schill W-B, Krämer H-J, Schlotzer E, Mayer K, Seeger W & Grimminger F (1998) N-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: Results of a double-blind, randomized, placebo-controlled multicenter trial. *Journal of the American Academy of Dermatology* **38**, 539–547.
- Pace-Asciak CR (1989) One-step rapid extractive methylation of plasma nonesterified fatty acids for gas chromatographic analysis. *Journal of Lipid Research* **30**, 451–454.
- Peterson J, Bihain BE, Bengtsson-Olivecrona G, Deckelbaum RJ, Carpentier YA & Olivecrona T (1990) Fatty acid control of lipoprotein lipase. A link between energy metabolism and lipid transport. *Proceedings of the National Academy of Science USA* **87**, 909–913.
- Ruzicka T & Grob E (1989) Pharmacologic effects of linoleic acid (LA) in skin and polymorphonuclear leukocytes. *Journal of Investigative Dermatology* **92**, 510.
- Schena D, Chieragato GC, de Gironcoli M, Girelli D, Olivieri O, Stanzial AM, Corrocher R, Bassi A, Ferrari S & Perazzoli P (1989) Increased erythrocyte membrane arachidonate and platelet malondialdehyde (MDA) production in psoriasis: normalization after fish-oil. *Acta Dermato-Venereologica Stockh* **146**(supplement), 42–44.
- Sola J, Godessart N & Vila L (1992) Epidermal cell-polymorphonuclear leukocyte cooperation in the formation of leukotriene B₄ by transcellular biosynthesis. *Journal of Investigative Dermatology* **98**, 333–339.
- Soyland E, Funk J, Rajka G, Sandberg M, Thune P, Rustad L, Helland S, Middelfart K, Odu S & Falk ES (1993) Effect of

- dieatry supplementation with very long chain *n*-3 fatty acids in patients with psoriasis. *New England Journal of Medicine* **328**, 1812–1816.
- von Schacky C & Weber PC (1985) Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acid in humans. *Journal of Clinical Investigation* **76**, 2446–2450.
- Yamazaki K, Hamazaki T, Yano S, Funada T & Ibuki F (1991) Changes in fatty acid composition in rat blood and organs after infusion of docosahexaenoic acid ethyl ester. *American Journal of Clinical Nutrition* **53**, 620–627.
- Ziboh VA, Cohen KA, Ellis CN, Miller C, Hamilton TA, Kragballe K, Hydrick CR & Voorhees JJ (1986) Modulation of clinical course of psoriatic subjects. *Archives of Dermatology* **122**, 1277–1282.