In vitro and *in vivo* effects of *n*-3 polyunsaturated fatty acids on human monocyte function

David A. Hughes

Department of Nutrition, Diet and Health, Institute of Food Research, Norwich Research Park, Norwich NR4 7UA, UK

The inhibitory effect of *n*-3 polyunsaturated fatty acids (PUFA) on cell-mediated immune responses has been recognized from epidemiological observations (Kromann & Green, 1980) as well as animal and human intervention studies (Maki & Newberne, 1992). Many human studies investigating potential mechanisms for this effect have concentrated on examining the influence of *n*-3 PUFA on the function of lymphocytes (see Calder, 1998) because of their central role in regulating immune responses, but considerably less attention has been given to the effect of dietary fatty acids on human monocytes.

Monocytes and macrophages

Monocytes account for between 3 and 6 % of the circulating leucocyte population. They belong to the mononuclear phagocyte system and originate in the bone marrow from stem cells. The monoblast and promonocyte give rise to monocytes, which remain very briefly in the bone marrow, and then enter the circulation where they remain for about 36–104 h. Monocytes then migrate into the tissues, where they mature and differentiate into macrophages ('big eaters') in response to environmental stimuli (Beelen *et al.* 1994). Monocytes and macrophages contribute to a wide range of host defence activities. Their best known function is the phago- and pinocytosis of micro-organisms, effete cells, debris and other waste products. They also display a highly-efficient cytotoxicity activity towards invading micro-organisms, virally-infected cells and tumour cells (Pryima, 1989). Activated monocytes produce a large variety of cytotoxic products, including pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and reactive oxygen species. Monocytes are also involved in initiating antigen-specific cell-mediated immune responses by taking up, processing and presenting antigens to helper T lymphocytes. The present paper reviews the studies that have investigated the effects of *n*-3 PUFA on these functions of human monocytes.

Effect of dietary *n*-3 polyunsaturated fatty acids intake on monocyte fatty acid composition

Dietary fish oils, rich in *n*-3 PUFA, are rapidly incorporated into the membrane phospholipids of circulating human monocytes, suggesting that they are likely to have an effect on several aspects of cell function. Two studies which have analysed purified monocytes, as opposed to mononuclear cells (which are a combination of monocytes and lymphocytes), have shown that moderate dietary supplementation with *n*-3 PUFA can significantly increase the cellular levels of these fatty acids within 2 weeks (Gibney & Hunter, 1993), with levels of eicosapentaenoic acid (20 : 5*n*-3; EPA) reaching a maximal accumulation after 6 weeks supplementation, whereas docosahexaenoic acid (22 : 6*n*-3; DHA) reached a peak at 18 weeks (Marangoni *et al.* 1993). During the post-supplementation period, EPA returned rapidly to pre-treatment levels in monocytes (although plasma levels remained significantly elevated from baseline after 24 weeks of washout), whilst levels of DHA declined more slowly (Marangoni *et al.* 1993).

Effect of *n*-3 polyunsaturated fatty acids on monocyte phagocytosis, cytotoxicity and chemotaxis

There have been very few studies of the effect of *n*-3 PUFA on these aspects of monocyte function using human material. Some animal studies suggest that fish oil can inhibit (Eicher & McVey, 1995) or does not affect (D'Ambola *et al.* 1991; Turek *et al.* 1994) phagocytosis by macrophages, but this has not been confirmed in human subjects. A reduction in superoxide production and other free radicals (which are inducers of cytotoxicity) by human monocytes following *ex vivo* stimulation was observed following 6 weeks dietary supplementation with 6 g *n*-3 PUFA/d (Fisher *et al.* 1990). This effect was associated with a reduction in monocyte stearic acid and arachidonic acid contents and an elevation in EPA and DHA contents.

Long-term supplementation (9 months) with 4 g *n*-3 PUFA/d significantly reduced human monocyte chemotaxis in response to autologous serum to the same extent as that seen after 6 weeks supplementation (Schmidt *et al.* 1992). However, more recently the same workers have reported that low-dose *n*-3 PUFA supplementation (0·65 g/d) for 12 weeks had no significant effect on monocyte chemotaxis (Schmidt *et al.* 1996). Analysis of the monocyte fatty acid composition showed an increase in EPA but not DHA following this level of supplementation, which might have some relevance to the lack of effect observed.

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HLA, human leucocyte antigen; ICAM-1, intercellular adhesion molecule-1; IL-1, interleukin-1; LFA, leucocyte-function associated antigen; MHC, major histocompatibility complex; PUFA, polyunsaturated fatty acids; TNF-α, tumour necrosis factor-α.

Corresponding author: Dr David A. Hughes, fax +44 (0)1603 255237, email davida.hughes@bbsrc.ac.uk

https://doi.org/10.1079/PNS19980076 Published online by Cambridge University Press

Effect of *n*-3 polyunsaturated fatty acids on monocyte cytokine production

IL-1β and TNF-α are two of the principal mediators of inflammation. They induce fever and the synthesis of acute-phase proteins by the liver, activate T and B lymphocytes and endothelial cells, and are involved in many other aspects of the acute-phase response (Dinarello, 1991). Following the original report by Endres *et al.* (1989), several other studies have also shown that dietary supplementation with *n*-3 PUFA can inhibit the *ex vivo* synthesis of IL-1β and TNF-α (for reviews, see Meydani & Dinarello, 1993; Blok *et al.* 1996; Endres & von Schacky, 1996). Recently, Caughey *et al.* (1996) demonstrated that a diet enriched with flaxseed oil (rich in α-linolenic acid, 18 : 3*n*-3, which can be elongated and desaturated in the body to form EPA) can inhibit the *ex vivo* production of these cytokines by approximately 30 % after 4 weeks. Supplementation with fish oil (9 g/d) for a further 4 weeks, whilst on the same diet, inhibited TNF-α and IL-1β synthesis by 74 and 80 % respectively. There was a significant inverse exponential relationship between TNF-α or IL-1β synthesis and mononuclear cell content of EPA. Cytokine production decreased as cellular EPA increased to approximately 1 g/100 g total fatty acids, but further increases in EPA content did not result in further decreases in cytokine production. Fish oil ingestion increased cellular EPA and DHA concentrations, whereas flaxseed oil ingestion increased cellular EPA but not DHA concentrations. It is possible, therefore, that the greater inhibition of cytokine production seen with fish oil, when compared with flaxseed oil ingestion, is due to the additional ingestion and tissue elevation of DHA concentrations. Caughey *et al.* (1996) suggest that *n*-3 PUFA may inhibit cytokine synthesis, at least in part, by inhibiting thromboxane A_2 synthesis. Mononuclear thromboxane A_2 synthesis was inhibited by flaxseed oil and fish oil, and treatment of human monocytes with thromboxane-receptor antagonists inhibited TNF-α synthesis, suggesting that thromboxane A_2 is a facilitator of cytokine synthesis in human monocytes.

Effect of *n*-3 polyunsaturated fatty acids on the antigen-presenting function of monocytes

Monocytes and macrophages initiate cell-mediated immune responses by processing and subsequently expressing antigens on their surface membranes for recognition by appropriate T-cells (Unanue & Cerottini, 1989). A prerequisite for this antigen-presenting cell function is the expression of major histocompatibility complex (MHC; which is known as the human leucocyte antigen (HLA) system in man) class II antigens, such as HLA-DR, HLA-DP and HLA-DQ (Bach, 1985). It has been shown that the T-cell proliferative response to antigen is proportional to the number of MHC class II molecules on the surface of antigen-presenting cells (Matis *et al.* 1983), and that the percentage of MHC class II-positive cells and the density of these molecules on the cell surface can alter the degree of immune responsiveness of an individual (Janeway *et al.* 1984).

In addition to requiring the expression of MHC class II molecules, cell–cell adhesion appears to be critical for the initiation of a primary immune response. There is increasing evidence that several adhesion receptor–ligand pairs can facilitate an immune response not only by enhancing adhesion, but by providing an additional distinct co-stimulatory signal. The binding of the adhesion molecule leucocyte-function-associated antigen-1 (LFA-1) to its ligand, intercellular adhesion molecule-1 (ICAM-1), has been shown to be capable of co-stimulating an immune response (Springer, 1990).

Several animal studies have shown that *n*-3 PUFA can inhibit the expression of Ia molecules, the murine equivalent of the human MHC class II molecules (Kelley *et al.* 1985; Mosquera *et al.* 1990; Huang *et al.* 1992). Dietary enrichment with EPA has also been shown to inhibit the ability of spleen cells to present antigens to murine helper T-cell clones, and *in vitro* pretreatment of splenocytes with EPA also resulted in inhibition of antigen-presenting-cell function (Fujikawa *et al.* 1992). Recently, it has been shown that dietary fish oil can diminish the ability of rat dendritic cells (another class of antigen-presenting cells) to present antigen to autologous spleen lymphocytes (Sanderson *et al.* 1997).

Using monocytes purified from blood samples from healthy volunteers, we observed that *in vitro* culture with EPA inhibits the expression of HLA-DR and ICAM-1 in a dose-dependent manner (Hughes *et al.* 1996*b*). In contrast, a significant increase in the expression of HLA-DR and -DP was observed on monocytes following incubation with DHA. Since it has been reported that synovial fluid monocytes obtained from patients with rheumatoid arthritis express elevated levels of MHC class II molecules (Firestein & Zvaifler, 1987), we also examined the effect of *n*-3 PUFA on activated monocytes, cultured in the presence of interferon-γ, to up-regulate the expression of MHC class II molecules on the monocytes. Both EPA and DHA significantly inhibited the expression of HLA-DR, -DP and ICAM-1 on the activated monocytes (Hughes *et al.* 1996*b*). In a dietary supplementation study, providing healthy volunteers with 1·5 g *n*-3 PUFA/d for 3 weeks, we also observed a significant inhibition of expression of these molecules on human peripheral-blood monocytes (Hughes *et al.* 1996*a*). Since EPA and DHA had exhibited opposing effects *in vitro* on surface-molecule expression on unstimulated monocytes, we subsequently investigated the combined effect of these fatty acids *in vitro*, when provided at the same ratio as that commonly found in fish oil supplement capsules (3 : 2, w/w). The combined fatty acids had no significant effect on the expression of HLA-DR on unstimulated monocytes, but the expression on interferon-γ-activated monocytes remained significantly inhibited. The expression of ICAM-1 and that of another adhesion molecule, LFA-3, on both unstimulated and activated cells was also significantly inhibited (Hughes & Pinder, 1997). Using the same *in vitro* system, the ability of interferon-γ-activated monocytes to present antigen to autologous lymphocytes was also significantly reduced following culture with the combined *n*-3 PUFA. Taken together, the results of these animal and human studies support the hypothesis that *n*-3 PUFA suppress cell-mediated immune responses, at least in part, by inhibiting antigen-presenting-cell function.

There are several mechanisms which may be involved in the modulatory effect of *n*-3 PUFA on surface-molecule expression. It is possible that the incorporation of these fatty

acids into the cell membrane can increase its fluidity and, thus, alter the expression of membrane proteins (Muller *et al.* 1983), possibly by influencing the vertical displacement of the proteins within the membrane. It has been shown that different proteins exhibit disparate changes in cell-surface-molecule expression following alterations in membrane fluidity (Muller & Krueger, 1986). This might explain why, in contrast to HLA-DR, ICAM-1 and LFA-3, no significant changes in HLA-DQ and LFA-1 expression were observed on unstimulated monocytes. In addition, we have previously shown that increasing the cholesterol content of human monocyte cell membranes, which causes a decrease in membrane fluidity, leads to a greater increase in the expression of HLA-DQ on resting monocytes than in the expression of HLA-DR and HLA-DP (Hughes *et al.* 1992). Interestingly, ICAM-1 and LFA-3 belong to the same family of structurally-related adhesion molecules, the immunoglobulin superfamily, whereas LFA-1 is a member of the integrin family. Thus, it is possible that the structural form of the surface molecule is important in determining its expression relative to the fluidity of the membrane.

Since PUFA are more susceptible to lipid peroxidation than are monounsaturated and saturated fatty acids, it is possible that an increase in monocyte cell membrane lipid peroxidation may affect the expression of cell surface molecules. It has already been demonstrated that free radicals can suppress the expression of HLA-DR (Gruner *et al.* 1986) and we have recently reported that dietary supplementation with the antioxidant carotenoid, β-carotene, can enhance the expression of HLA-DR, ICAM-1 and LFA-3 on human peripheral-blood monocytes (Hughes *et al.* 1997).

A further possibility is that EPA and DHA are directly or indirectly influencing the expression of mRNA for the various cell surface molecules. It has recently been shown that DHA can inhibit the expression of Ia molecules on murine macrophages *in vitro*, in parallel with a decrease in Ia mRNA levels (Khair-El-Din *et al.* 1995). Whether similar effects occur in human monocytes, and whether any effect observed is related to an effect on the transcription factor, nuclear factor-kappa B, which regulates the transcription of mRNA for many cell surface molecules and cytokines (Baldwin, 1996), is currently under investigation.

Potential influence of *n*-3 polyunsaturated fatty acids effects on monocytes in chronic inflammatory disorders

The inhibitory effect of *n*-3 PUFA ingestion on monocyte and macrophage activity may be relevant to a number of chronic inflammatory conditions. There are two disorders with known monocyte involvement in their pathogenesis and progression, rheumatoid arthritis and atherosclerosis.

Rheumatoid arthritis

Cytokines have a key role in the pathogenesis of rheumatoid arthritis, and inhibition of TNF-α and IL-1β is one of the therapeutic targets in the treatment of this and other chronic inflammatory conditions. A randomized double-blind trial of chimeric monoclonal antibody to TNF has shown promising results in terms of a reduction in clinical symptoms and in levels of serum C-reactive protein (Elliott *et al.* 1994). However, at present, the potential risks of this form of immunotherapy, and whether disease outcome is affected by it, remain unclear. Since plasma levels of IL-1 have been shown to correlate with disease activity in patients with active rheumatoid arthritis (Eastgate *et al.* 1988), the ability of dietary fish oil supplementation to suppress the synthesis of this cytokine (to the same degree as is achievable by administration of glucocorticoids or cyclosporin A, which have well-known adverse effects, particularly during long-term administration) suggests that the ability of *n*-3 PUFA to modulate secretion of these cytokines within the synovium merits further investigation. Reduced plasma levels of IL-1 in patients with rheumatoid arthritis have been observed following fish oil supplementation (Esperson *et al.* 1992). The ability of *n*-3 PUFA to inhibit the antigen-presenting function of activated monocytes is another potential mechanism by which the inflammatory activity at the localized sites of disease might be reduced. The striking inhibition of MHC class II molecules and ICAM-1 expression by EPA and DHA on interferon-γ stimulated monocytes may be particularly relevant to rheumatoid arthritis, since patients with this disorder have been shown to have abnormally-elevated expression of both MHC class II molecules (Firestein & Zvaifler, 1987) and ICAM-1 (Wicks *et al.* 1992) in chronically inflamed joints. A corresponding reduction in antigen-presenting function might lead to reduced helper T-cell activation, thus decreasing both the production of inflammatory cytokines and the production of antibodies by synovial B-cells.

Atherosclerosis

The cardiovascular disease risk and mortality-lowering effect of ingesting *n*-3 fatty acids has been recognized from both population studies (Kromann & Green, 1980) and prospective trials (Burr *et al.* 1989), at least in part because of reduced atherosclerosis (Newman *et al.* 1993). There is increasing evidence of a chronic immune and inflammatory involvement in the formation of atherosclerotic lesions (Ross, 1993), and the presence of chronically-stimulated T-cells within lesions, and the expression of MHC class II molecules on lesional monocytes–macrophages indicates that these cells are actively participating in the local immune response occurring during atherogenesis (Hansson *et al.* 1989). Supplementation studies have shown that EPA and DHA are incorporated into the lipids of advanced atherosclerotic plaques in man (Rapp *et al.* 1991), and it is possible that a reduced expression of MHC class II molecules might inhibit the antigen-presenting function of the local macrophages, thereby delaying, if not preventing, lesion development. In addition, the reduced production of free radicals by monocytes following fish oil supplementation (D'Ambola *et al.* 1991) might also impair the capability of macrophages derived from monocytes to promote oxidation of LDL-cholesterol, a key component in the pathogenesis of atherosclerosis (Ross, 1993).

Concluding remarks

Although the number of studies investigating the effects of *n*-3 PUFA on human monocytes is considerably less than

https://doi.org/10.1079/PNS19980076 Published online by Cambridge University Press

that on lymphocytes, most suggest that these fatty acids inhibit a variety of inflammatory activities of these important immune cells. These effects are probably mediated by a variety of mechanisms, including alterations in (1) eicosanoid synthesis, (2) plasma membrane fluidity, (3) gene expression and (4) an increased susceptibility to lipid peroxidation. The levels of *n*-3 PUFA ingestion used in the studies described may not be directly relevant in devising recommended intakes for the healthy individual but the studies do provide useful information for the design of nutritionally-based therapeutic strategies. Further mechanistic studies are warranted, coupled with lower-dose dietary supplementation trials, in order to further our understanding of the effects of *n*-3 PUFA on monocyte function in health and disease.

References

Bach FH (1985) Class II genes and products of the HLA-D region. *Immunology Today* **6**, 89–94.

Baldwin AS Jr (1996) The NF-κB and IκB proteins: new discoveries and insights. *Annual Review of Immunology* **14**, 649–681.

Beelen RHJ, Betjes MGH & Kamperdijk EWA (1994) Macrophages: general aspects. In *Immunopharmacology of Macrophages and other Antigen-presenting Cells*, pp. 1–6 [CAFM Bruijnzeel-Koomen and ECM Hoefsmit, editors]. London: Academic Press.

Blok WL, Katan MB & van der Meer JWM (1996) Modulation of inflammation and cytokine production by dietary (*n*-3) fatty acids. *Journal of Nutrition* **126**, 1515–1533.

Burr ML, Gilberet JF, Holliday RM, Elwood PC, Fehily AM, Rogers S, Sweetnam PM & Deadman NM (1989) Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* **ii**, 757–761.

Calder PC (1998) Dietary fatty acids and lymphocyte functions. *Proceedings of the Nutrition Society* **57**, 487–502.

Caughey GE, Mantzioris E, Gibson RA, Cleland LG & James MJ (1996) The effect of human tumour necrosis factor α and interleukin-1β production of diets enriched in *n*-3 fatty acids from vegetable oil or fish oil. *American Journal of Clinical Nutrition* **63**, 116–122.

D'Ambola JB, Aeberhard EE, Trang N, Gaffar S, Barrett CT & Sherman MP (1991) Effect of dietary (*n*-3) and (*n*-6) fatty acids on *in vivo* pulmonary bacterial clearance by neonatal rabbits. *Journal of Nutrition* **121**, 1262–1269.

Dinarello CA (1991) Interleukin-1 and interleukin-1 antagonism. *Blood* **77**, 1627–1652.

Eastgate JA, Wood NC, di Giovine FS, Symons JA, Grinlinton FM & Duff GW (1988) Correlation of plasma interleukin-1 levels with disease activity in rheumatoid arthritis. *Lancet* **ii**, 706–709.

Eicher SD & McVey DS (1995) Dietary modulation of Kupffer cell and splenocyte function during a *Salmonella typhimurium* challenge in mice. *Journal of Leukocyte Biology* **58**, 32–39.

Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Bijl H & Woody JN (1994) Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* **344**, 1105–1110.

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 (1989) The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumour necrosis factor by mononuclear cells. *New England Journal of Medicine* **320**, 265–271.

Endres S & von Schacky C (1996) *n*-3 Polyunsaturated fatty acids and human cytokine synthesis. *Current Opinion in Lipidology* **7**, 48–52.

Esperson GT, Grunnet N, Lervang HH, Nielsen GL, Thomsen BS, Faarvang KL, Dyerberg J & Ernst E (1992) Decreased interleukin-1 beta levels in plasma from rheumatoid arthritis patients after dietary supplementation with *n*-3 polyunsaturated fatty acids. *Clinical Rheumatology* **11**, 393–395.

Firestein GS & Zvaifler NJ (1987) Peripheral blood and synovial fluid monocyte activation in inflammatory arthritis. I. A cytofluorographic study of monocyte differentiation antigens and class II antigens and their regulation by gamma-interferon. *Arthritis and Rheumatism* **30**, 857–863.

Fisher M, Levine PH, Weiner BH, Johnson MH, Doyle EM, Ellis PA & Hoogasian JJ (1990) Dietary *n*-3 fatty acid supplementation reduces superoxide production and chemiluminescence in a monocyte-enriched preparation of leucocytes. *American Journal of Clinical Nutrition* **51**, 804–808.

Fujikawa M, Yamashita N, Yamazaki K, Sugiyama E, Suzuki H & Hamazaki T (1992) Eicosapentaenoic acid inhibits antigen-presenting cell function of murine splenocytes. *Immunology* **75**, 330–335.

Gibney MJ & Hunter B (1993) The effects of short- and long-term supplementation with fish oil on the incorporation of n-3 polyunsaturated fatty acids into cells of the immune system in healthy volunteers. *European Journal of Clinical Nutrition* **47**, 255–259.

Gruner S, Volk H-D, Falck P & Baehr RV (1986) The influence of phagocytic stimuli on the expression of HLA-DR antigens; role of reactive oxygen intermediates. *European Journal of Immunology* **16**, 212–215.

Hansson GK, Holm J & Jonasson L (1989) Detection of activated T lymphocytes in the human atherosclerotic plaque. *American Journal of Pathology* **135**, 169–175.

Huang SC, Misfeld ML & Fritshe KL (1992) Dietary fat influences Ia expression and immune cell populations in the murine peritoneum and spleen. *Journal of Nutrition* **122**, 1219–1231.

Hughes DA & Pinder AC (1997) *N*-3 polyunsaturated fatty acids modulate the expression of functionally associated molecules on human monocytes and inhibit antigen presentation *in vitro*. *Clinical and Experimental Immunology* **110**, 516–523.

Hughes DA, Pinder AC, Piper Z, Johnson IT & Lund EK (1996*a*) Fish oil supplementation inhibits the expression of major histocompatibility complex class II molecules and adhesion molecules on human monocytes. *American Journal of Clinical Nutrition* **63**, 267–272.

Hughes DA, Southon S & Pinder AC (1996*b*) (n-3) Polyunsaturated fatty acids modulate the expression of functionally associated molecules on human monocytes in vitro. *Journal of Nutrition* **126**, 603–610.

Hughes DA, Townsend PJ & Haslam PL (1992) Enhancement of the antigen-presenting function of monocytes by cholesterol: possible relevance to inflammatory mechanisms in extrinsic allergic alveolitis and atherosclerosis. *Clinical and Experimental Immunology* **87**, 279–286.

Hughes DA, Wright AJA, Finglas PM, Peerless ACJ, Bailey AL, Astley SB, Pinder AC & Southon S (1997) The effect of beta-carotene supplementation on the immune function of blood monocytes from healthy male non-smokers. *Journal of Laboratory and Clinical Medicine* **129**, 309–317.

Janeway CA, Bottomly K, Babich J, Conrad P, Conzen S, Jones B, Kaye J, Katz M, McVay L, Murphy DB & Tite J (1984) Quantitative variation in Ia antigen expression plays a central role in immune regulation. *Immunology Today* **5**, 99–104.

Kelley VE, Ferretti A, Izui S & Strom TB (1985) A fish oil diet rich in eicosapentaenoic acid reduces cyclooxygenase metabolites,

and suppresses lupus in MRL-lpr mice. *Journal of Immunology* **134**, 1914–1919.

Khair-El-Din TA, Sicher SC, Vazquez MA, Wright WJ & Lu CY (1995) Docosahexaenoic acid, a major constituent of fetal calf serum and fish oil diets, inhibits IFN-γ-induced Ia-expression by murine macrophages *in vitro*. *Journal of Immunology* **154**, 1296–1306.

Kromann A & Green A (1980) Epidemiological studies in the Upernavik district, Greenland. Incidence of some chronic diseases 1950–1974. *Acta Medica Scandinavica* **208**, 401–406.

Maki PA & Newberne PM (1992) Dietary lipids and immune function. *Journal of Nutrition* **122**, 610–614.

Marangoni F, Angeli MT, Colli S, Eligini S, Tremoli E, Sirtori CR & Galli C (1993) Changes of n-3 and n-6 fatty acids in plasma and circulating cells of normal subjects, after prolonged administration of 20 : 5 (EPA) and 22 : 6 (DHA) ethyl esters and prolonged washout. *Biochimica et Biophysica Acta* **1210**, 55–62.

Matis LA, Glimcher LH, Paul WE & Schwartz RH (1983) Magnitude of response of histocompatibility-restricted T-cell clones is a function of the product of the concentration of antigen and Ia molecules. *Proceedings of the National Academy of Sciences USA* **80**, 6019–6023.

Meydani SN & Dinarello CA (1993) Influence of dietary fatty acids on cytokine production and its clinical implications. *Nutrition in Clinical Practice* **8**, 65–72.

Mosquera J, Rodriguez-Iturbe B & Parra G (1990) Fish oil dietary supplementation reduces Ia expression in rat and mouse peritoneal macrophages. *Clinical Immunology and Immunopathology* **56**, 124–129.

Muller CP & Krueger GRF (1986) Modulation of membrane proteins by vertical phase separation and membrane lipid fluidity. Basis for a new approach to tumor immunotherapy. *Anticancer Research* **6**, 1181–1194.

Muller CP, Stephany DA, Shinitzky M & Wunderlich JR (1983) Changes in cell-surface expression of MHC and Thy-1·2 determinants following treatment with lipid modulating agents. *Journal of Immunology* **131**, 1356–1362.

Newman W, Middaugh J, Propst M & Rogers D (1993) Atherosclerosis in Alaska natives and non-natives. *Lancet* **341**, 1056–1057.

Pryima J (1989) Immunoregulatory functions of monocytes. In *Human Monocytes*, pp. 237–246 [M Zembala and GL Asherson, editors]. London: Academic Press.

Rapp JH, Connor WE, Lin DS & Porter JM (1991) Dietary eicosapentaenoic acid and docosahexaenoic acid from fish oil. Their incorporation into advanced human atherosclerotic plaques. *Arteriosclerosis and Thrombosis* **11**, 903–911.

Ross R (1993) The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* **362**, 801–809.

Sanderson P, Macpherson GG, Jenkins CH & Calder PC (1997) Dietary fish oil diminishes the antigen presentation activity of rat dendritic cells. *Biochemical Society Transactions* **25**, 351S.

Schmidt EB, Varming K, Moller JM, Bulow Pedersen I, Madsen P & Dyerberg J (1996) No effect of a very low dose of *n*-3 fatty acids on monocyte function in healthy humans. *Scandinavian Journal of Clinical and Laboratory Investigation* **56**, 87–92.

Schmidt EB, Varming K, Pederson JO, Lervang HH, Grunnet N, Jersild C & Dyerberg J (1992) Long-term supplementation with *n*-3 fatty acids, II: effect on neutrophil and monocyte chemotaxis. *Scandinavian Journal of Clinical and Laboratory Investigation* **52**, 229–236.

Springer TA (1990) Adhesion receptors of the immune system. *Nature* **346**, 425–434.

Turek JJ, Schoenlein IA, Clark LK & van Alstine WG (1994) Dietary polyunsaturated fatty acid effects on immune cells of the porcine lung. *Journal of Leukocyte Biology* **56**, 599–604.

Unanue ER & Cerottini J-C (1989) Antigen presentation. *FASEB Journal* **3**, 2496–2502.

Wicks IP, Leizer T, Wawryk SO, Novotny JR, Hamilton J, Vitti G & Boyd AW (1992) The effect of cytokines on the expression of MHC antigens and ICAM-1 by normal and transformed synoviocytes. *Autoimmunity* **12**, 13–19.

https://doi.org/10.1079/PNS19980076 Published online by Cambridge University Press