ABSTRACT: The fatty acid composition of inflammatory and immune cells is sensitive to change according to the fatty acid composition of the diet. In particular, the proportion of different types of polyunsaturated fatty acids (PUFA) in these cells is readily changed, and this provides a link between dietary PUFA intake, inflammation, and immunity. The n-6 PUFA arachidonic acid (AA) is the precursor of prostaglandins, leukotrienes, and related compounds, which have important roles in inflammation and in the regulation of immunity. Fish oil contains the n-3 PUFA eicosapentaenoic acid (EPA). Feeding fish oil results in partial replacement of AA in cell membranes by EPA. This leads to decreased production of AA-derived mediators. In addition, EPA is a substrate for cyclooxygenase and lipoxygenase and gives rise to mediators that often have different biological actions or potencies than those formed from AA. Animal studies have shown that dietary fish oil results in altered lymphocyte function and in suppressed production of proinflammatory cytokines by macrophages. Supplementation of the diet of healthy human volunteers with fish oil-derived n-3 PUFA results in decreased monocyte and neutrophil chemotaxis and decreased production of proinflammatory cytokines. Fish oil feeding has been shown to ameliorate the symptoms of some animal models of autoimmune disease. Clinical studies have reported that fish oil supplementation has beneficial effects in rheumatoid arthritis, inflammatory bowel disease, and among some asthmatics, supporting the idea that the n-3 PUFA in fish oil are anti-inflammatory and immunomodulatory.


THE IMMUNE SYSTEM

The immune system acts to protect the host from infectious agents that exist in the environment (bacteria, viruses, fungi, parasites) and from other noxious insults. The immune system has two functional divisions, i.e., the innate (or natural) immune system and the acquired (also termed specific or adaptive) immune system. Both components of immunity involve various blood-borne factors and cells (Table 1). These cells are generally termed leukocytes (or white blood cells).

Abbreviations: AA, arachidonic acid; ALNA, α-linolenic acid; COX, cyclooxygenase; DGLA, dihomo-γ-linolenic acid; DHA, docosahexaenoic acid; DTH, delayed-type hypersensitivity; EPA, eicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; HLA, human leukocyte antigen; HPETE, hydroperoxyeicosatetraenoic acid; IFN, interferon; Ig, immunoglobulin; IL, interleukin; KLH, keyhole limpet hemocyanin; 5-LOX, 5-lipoxygenase; LT, leukotriene; MHC, major histocompatibility complex; NK, natural killer; PG, prostaglandin; Th, helper T cells; TNF, tumor necrosis factor.

Leukocytes fall into two broad categories, i.e., phagocytes, including granulocytes (neutrophils, basophils, eosinophils), monocytes and macrophages, and lymphocytes. Lymphocytes are classified as T lymphocytes, B lymphocytes and natural killer (NK) cells. T lymphocytes are further divided into helper T (Th) cells (these are distinguished by the presence of the molecule CD4 on their surface) and cytotoxic T cells (these are distinguished by the presence of CD8 on their surface). All cells of the immune system originate in bone marrow. They are found circulating in the bloodstream, organized into lymphoid organs such as the thymus, spleen, and lymph nodes, or dispersed in other locations around the body.

Innate and Acquired Immunity

Innate immunity is the first line of defense against infectious agents. It is present before exposure to pathogens and its activity is not enhanced by such exposures. Innate immunity is concerned with preventing entry of infectious agents into the body and, if they do enter, with their rapid elimination. Elimination can occur as follows: (i) by direct destruction of pathogens by complement, by toxic chemicals (e.g., superoxide radicals and hydrogen peroxide) released by phagocytes, or by toxic proteins released by NK cells; and (ii) by engulfment of pathogens by the process of phagocytosis, which is made more efficient by coating the invading pathogen with host proteins such as complement or antibodies, and their subsequent destruction.

Acquired immunity involves the specific recognition of molecules (antigens) on an invading pathogen, which distinguishes it as being foreign to the host. The recognition of antigens is by antibodies (produced by B lymphocytes) and by T lymphocytes. However, in contrast to B lymphocytes, T lymphocytes are able to recognize only antigens displayed on cell surfaces. Therefore, infection of a cell by an intracellular pathogen is signaled to T lymphocytes by cell surface expression of peptide fragments derived from the pathogen. These fragments are transported to the surface of the infected cell and expressed there in conjunction with proteins termed major histocompatibility complex (MHC). It is the combination of the pathogen-derived peptide fragment bound to MHC that is recognized by T lymphocytes. There are two classes of MHC, MHC I and MHC II, and the source of the peptide bound to each differs. MHC I binds peptides that originate from pathogen proteins synthesized within the host cell cytosol; typically, these are from viruses or certain bacteria. The peptides bound to MHC II are derived from pathogens that have been phagocytosed by macrophages or endocytosed by antigen-presenting cells (macrophages, dendritic cells, B lymphocytes).
The MHC-peptide complex is recognized by the T-cell receptor on T lymphocytes. T lymphocytes expressing CD8 recognize MHC I, whereas T lymphocytes expressing CD4 recognize MHC II. Thus, intracellular pathogens stimulate cytotoxic T lymphocytes to destroy the infected cell, whereas extracellular pathogens stimulate a helper T cell–mediated response.

The acquired immune system includes a component of memory, such that if the antigen is encountered again (i.e., there is reinfection), the response is faster and stronger than the initial response. Although the immune system as a whole can recognize tens of thousands of antigens, each lymphocyte can recognize only one antigen; thus the number of lymphocytes specific for a particular antigen must be very low. However, when an antigen is encountered, it binds to the small number of lymphocytes that recognize it and causes them to divide so as to increase the number of cells that are capable of mounting a response to the antigen; this is the process termed lymphocyte expansion or proliferation. B lymphocytes proliferate and mature into antibody-producing cells (plasma cells), and T lymphocytes proliferate and are able to directly destroy virally infected cells (cytotoxic T lymphocytes) or control the activity of other cells involved in the response (helper T cells). The B lymphocyte response to antigen is termed humoral immunity, and the T cell response is termed cell-mediated immunity.

Communication Within the Immune System

Communication within the acquired immune system and between the innate and acquired systems is brought about by direct cell-to-cell contact involving adhesion molecules and by the production of chemical messengers. Chief among these chemical messengers are proteins called cytokines, which can act to regulate the activity of the cell that produced the cytokine and/or of other cells. Each cytokine can have multiple activities on different cell types. Cytokines act by binding to specific receptors on the cell surface and thereby induce changes in growth, development, or activity of the target cell.

Tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 are among the most important cytokines produced by monocytes and macrophages. These cytokines activate neutrophils, monocytes, and macrophages to initiate bacterial and tumor cell killing, increase adhesion molecule expression on the surface of neutrophils and endothelial cells, stimulate T and B lymphocyte proliferation, upregulate MHC, and initiate the production of other cytokines (Fig. 1). Thus, TNF, IL-1, and IL-6 are mediators of both natural and acquired immunity and are an important link between them. In addition, these cytokines mediate the systemic effects of inflammation such as fever, loss of appetite, mobilization of protein and fat, and acute phase protein synthesis (Fig. 1).

Helper T lymphocytes are subdivided functionally according to the pattern of cytokines they produce (Fig. 2). It is believed that helper T cells that have not previously encountered antigen produce mainly IL-2 upon initial encounter with antigen. These cells may differentiate into a population some-
times referred to as Th0 cells, which differentiate further into either Th1 or Th2 cells (Fig. 2). This differentiation is regulated by cytokines as follows: IL-12 and interferon-γ (IFN-γ) promote the development of Th1 cells, whereas IL-4 promotes the development of Th2 cells (Fig. 2). Th1 and Th2 themselves have relatively restricted profiles of cytokine production, i.e., Th1 cells produce IL-2 and IFN-γ, which activate macrophages, NK cells, and cytotoxic T lymphocytes and are the principal effectors of cell-mediated immunity (Fig. 2). Interactions with bacteria, viruses, and fungi tend to induce Th1 activity. Because Th1 cytokines activate monocytes and macrophages, these cytokines may be regarded as proinflammatory. Th2 cells produce IL-4, which stimulates immunoglobulin (Ig) E production by B lymphocytes, IL-5, an eosinophil-activating factor, and IL-10, and which together with IL-4 suppresses cell-mediated immunity (Fig. 2). Th2 cells are responsible for defense against helminthic parasites, which is due to IgE-mediated activation of mast cells and basophils. Because Th2 cytokines suppress Th1 responses, these cytokines may be regarded as anti-inflammatory. An imbalance or dysregulation between the Th1- and Th2-type responses is a characteristic of many human diseases (2).

**Inflammation**

Inflammation is the body’s immediate response to infection or injury. It is typified by redness, swelling, heat, and pain. These occur as a result of increased blood flow, increased permeability across blood capillaries, which permits large molecules (e.g., complement, antibodies, cytokines) to leave the bloodstream and cross the endothelial wall, and increased movement of leukocytes from the bloodstream into the surrounding tissue. Thus, inflammation is part of the normal, innate immune response.

**Integration of the Immune Response**

The innate and acquired immune responses are integrated according to the direct cell-to-cell and cytokine interactions that result from the presence of a particular stimulus. The innate response, including its inflammatory component, reacts initially to the stimulus, acting directly to eliminate it by the activities of complement or phagocytosis, for example. Cytokines produced by the cells involved in the innate response, especially monocytes and macrophages, will regulate this response and also act systemically on the liver to promote acute phase protein synthesis, on skeletal muscle and adipose tissue to promote proteolysis and lipolysis, respectively (this is believed to be the body’s way of providing fuels to the immune system), and on the brain to reduce appetite and induce fever (Fig. 3). These cytokines will also interact with T lymphocytes. Antigen-presenting cells, which include activated monocytes and macrophages, will present antigen to T lymphocytes and thus the acquired immune response will be triggered (Fig. 3). Now there will be a cell-mediated response to the antigen. T lymphocytes will produce cytokines, which will regulate the activity of the cells involved in the innate response (monocytes, macrophages, NK cells), promote the proliferation of B and T lymphocytes, and promote antibody production by B lymphocytes. By virtue of the integrated innate and acquired responses, the source of the antigen should be eliminated and a component of immunological memory will remain (Fig. 3).
The Immune System in Health and Disease

Clearly, a well-functioning immune system is essential to health. It serves to protect the host from the effects of ever-present pathogenic organisms. Cells of the immune system also have a role in identifying and eliminating cancer cells. There are, however, some detrimental effects of the immune system, including the following:

(i) In the course of its activity to recognize and eliminate foreign antigens, the immune system is responsible for the rejection of transplanted tissues.

(ii) In some individuals, the immune system appears to recognize host antigens as “non-self” rather than as “self.” As a result, an immune response to host tissues is generated and this leads to tissue damage. This is the characteristic of so-called chronic inflammatory or autoimmune diseases. Such diseases are linked to genes coding for proteins involved in antigen presentation or recognition such as the MHC II proteins and the T-cell receptor; thus there is a genetic predisposition to these diseases. These diseases are typified by an ongoing chronic inflammation involving the proinflammatory cytokines produced by monocytes and macrophages and by a dysregulated Th1 lymphocyte response. Examples of this type of disease include rheumatoid arthritis, type-1 diabetes, Crohn’s disease, psoriasis, and multiple sclerosis.

(iii) The immune system of some individuals can become sensitized to usually benign antigens from the environment and can respond inappropriately to them. Such antigens can include components of foods or of so-called allergens (e.g., cat or dog fur, house dust mite, some pollens), such that this response can lead to allergies, asthma, and related atopic diseases. Although these diseases are often termed chronic inflammatory diseases, they have a different immune basis from the diseases described above, although again they are typified by inappropriate recognition of and/or responses to antigens. However, atopic diseases are characterized by a dysregulated Th2 lymphocyte response such that excessive amounts of IL-4, IL-5, and IL-10 are found. IL-10 suppresses the Th1 response, IL-4 stimulates IgE production by B lymphocytes (IgE promotes histamine release from mast cells), and IL-4 and IL-5 activate eosinophils, which are involved in the persistent inflammation that is a component of these diseases.

(iv) The innate immune system becomes activated as a result of trauma and surgery. This response is characterized by excess production of the proinflammatory cytokines and, if it persists, it can damage organs, causing their failure and leading to complications and sometimes death.

EICOSANIODS: A LINK AMONG POLYUNSATURATED FATTY ACIDS, INFLAMMATION, AND IMMUNITY

Eicosanoid Precursors and Synthesis

Eicosanoids are a second group of chemical messengers that act within the immune system. These compounds provide a link among polyunsaturated fatty acids (PUFA), inflammation, and immune function. Eicosanoids are synthesized from PUFA, in particular dihomo-γ-linolenic acid (DGLA; 20:3n-6), arachidonic acid (AA; 20:4n-6), and eicosapentaenoic acid (EPA; 20:5n-3). Eicosanoids include prostaglandins (PG), thromboxanes, leukotrienes (LT), lipoxins, hydroperoxyeicosatetraenoic acids (HPETE), and hydroxyeicosatetraenoic acids (HETE). The fatty acid precursor for eicosanoid synthesis is released from cell membrane phospholipids, usually by the action of phospholipase A2 activated in response to a cellular stimulus. Because the membranes of most immune cells contain large amounts of AA, compared with DGLA and EPA, AA is usually the principal precursor for eicosanoid synthesis.

Metabolism of AA by cyclooxygenase (COX) gives rise to the 2-series PG and thromboxanes (Fig. 4). There are two isoforms of COX; COX-1 is a constitutive enzyme and COX-2, which is induced in immune cells as a result of stimulation, is responsible for the markedly elevated production of PG that occurs upon cellular activation. There are at least 16 different 2-series PG, and these are formed in a cell-specific manner. For example, monocytes and macrophages produce large amounts of PGE2 and PGF2, neutrophils produce moderate amounts of PGE2, and mast cells produce PGD2.

Metabolism of AA by the 5-lipoxygenase (5-LOX) pathway gives rise to hydroxy and hydroperoxy derivatives (5-HETE and 5-HPETE, respectively), and the 4-series leukotrienes (LT), LTA4, B4, C4, D4 and E4 (Fig. 4). 5-LOX is found in mast cells, monocytes, macrophages, and granulocytes. The 12-LOX enzyme is found in platelets and some epithelial cells, and the 15-LOX is found in some epithelial cells.

Roles for Eicosanoids in Inflammation and Immunity

PGE2 has a number of proinflammatory effects, including induction of fever and erythema, increasing vascular permeability and vasodilation, and enhancing pain and edema caused by other agents such as histamine. PGE2 suppresses lympho-
cyte proliferation and NK cell activity and inhibits production of TNF-α, IL-1, IL-6, IL-2, and IFN-γ; thus, in these respects, PGE₂ does not appear to affect the production of the Th2 cytokines IL-4 and IL-10 directly, but it does promote IgE production by B lymphocytes (Fig. 5). LTβ₄ increases vascular permeability, enhances local blood flow, is a potent chemotactic agent for leukocytes, induces release of lysosomal enzymes, enhances generation of reactive oxygen species, inhibits lymphocyte proliferation, and promotes NK cell activity. LT (4-series) also regulate production of proinflammatory cytokines; for example, LTβ₄ enhances production of TNF, IL-1, IL-6, IL-2, and IFN-γ (Fig. 5). 5-HETE enhances whereas 15-HETE inhibits lymphocyte proliferation. Thus, AA gives rise to a range of mediators that have opposing effects to one another so that the overall physiological effect will be governed by the concentration of those mediators, the timing of their production, and the sensitivities of target cells to their effects.

Feeding animals or humans increased amounts of fish oil, which contains EPA and its derivative docosahexaenoic acid (DHA; 22:6n-3), results in a decrease in the amount of AA in the membrane phospholipids of cells involved in inflammation and immunity (Fig. 6). In addition, long-chain n-3 PUFA appear to inhibit the release of AA from membrane phospholipids perhaps by inhibition of phospholipases (4). EPA also competes with AA for the active sites of COX and 5-LOX. Thus, fish oil feeding results in a decreased capacity of immune cells to synthesize eicosanoids from AA (Figs. 7, 8). In addition, EPA is able to act as a substrate for both COX and 5-LOX, giving rise to derivatives that have a different structure from those produced from AA (i.e., 3-series PG and 5-series LT) (Figs. 7, 8). Thus, the EPA-induced suppression in the production of AA-derived eicosanoids is mirrored by an elevation in the production of EPA-derived eicosanoids (Fig. 7). The eicosanoids produced from AA are considered to be less biologically potent than the analogs synthesized from AA, although the full range of biological activities of these compounds has not been investigated. The best example of differential immunological potencies of eicosanoids produced from AA and EPA is that of LTβ₄ vs. LTβ₅. LTβ₄ is at least 10-fold less potent as a neutrophil chemoattractant than LTβ₄ and, on this basis, can be considered to be considerably less proinflammatory. One other aspect of the formation of alternative eicosanoids to those produced from AA is that they will share the same receptor on target cells and therefore will act to antagonize the AA-derived mediators (Fig. 8).

**PUFA AND IMMUNE FUNCTION**

**Linoleic Acid (18:2n-6) and Immune Function**

In *vitro* studies. Linoleic acid enhanced superoxide release from neutrophils and macrophages (7–10) and promoted neutrophil adhesion to endothelial cells (11), suggesting that it possesses proinflammatory effects. In contrast, linoleic acid inhibited the proliferation of rodent and human lymphocytes (12–16) and decreased the production of IL-2 by mitogen-stimulated rat and human lymphocytes (13,14), suggesting that it is potentially immunosuppressive.

Animal feeding studies. Essential fatty acid deficiency impaired the ability of mice to produce IgG and IgM in response to sheep red blood cells (17); this response was restored by feeding diets containing 130, 500, or 700 g corn oil/kg (17). In contrast to this apparent enhancing effect of linoleic acid on antibody production, dietary linoleic acid was found to impair the production of antibodies, including IgG and IgM, after antigenic challenges, compared with feeding diets containing low fat or high saturated fat (beef tallow, coconut oil) (18,19). Compared with diets high in saturated fatty acids, feeding rodents high-fat diets rich in linoleic acid decreased mitogen-stimulated lymphocyte proliferation and NK cell activity in some studies (see Ref. 20 for references). These studies suggest that very high levels of linoleic acid in the rodent diet impair cell-mediated and antibody responses. However, modest changes in the amount of linoleic acid in the rat diet did not markedly affect lymphocyte proliferation or NK cell activity (21).

**Human studies.** Surprisingly, few human studies have investigated the immunological effect of linoleic acid. The most detailed of the studies that have been performed are those of Kelley *et al* (22,23), which involved providing volunteers with low-fat diets (25% energy as fat) that were rich (12.9% of energy) or poor in linoleic acid (3.5% of energy). No differences were observed in the responses of lymphocytes to various T-cell mitogens, in circulating IgM, IgG, IgE, or IgA levels, or in the delayed-type hypersensitivity (DTH) response to seven recall antigens. Yaqoob *et al* (24) included a group consuming 9 g encapsulated sunflower oil/d for 12 wk in their study. This had no effect on lymphocyte proliferation,
NK cell activity, or production of TNF-α, IL-1α, IL-1β, IL-2, and IFN-γ by mononuclear cells. These studies suggest a limited effect of linoleic acid (at a level ≥3.5% of dietary energy) on human immune function. However, in another study, the low-fat diet–induced increase in human NK cell activity (25) was reversed by adding 15 g safflower oil/d to the diet for 2 mo (26). Furthermore, the NK cell activity of blood lymphocytes from elderly Danish subjects correlated negatively with linoleic acid intake and with serum levels of linoleic acid (27).

AA and Immune Function

In vitro studies. AA enhanced superoxide release from neutrophils and macrophages (7–10), promoted neutrophil adhesion to endothelial cells (11), and increased IL-1β production by a monocyctic cell line (28) and by human monocytes (29). Thus, AA exhibits proinflammatory effects in vitro. AA inhibited the proliferation of rodent, pig, and human lymphocytes (12–16,30–32) and decreased the production of IL-2 by mitogen-stimulated rat and human lymphocytes (13,14), suggesting that it is potentially immunosuppressive.

Animal feeding studies. Feeding mice a diet containing 20 g safflower oil plus 10 g AA/kg did not affect spleen lymphocyte proliferation or IL-2 production compared with feeding a diet containing safflower oil (30 g/kg) (33). Inclusion of 4.4 g AA/100 g fatty acids in the rat diet did not significantly affect spleen lymphocyte proliferation, NK cell activity, or the graft vs. host response, despite the increased capacity of immune cells from rats fed AA to produce PGE2 (34). These studies suggest that even significant amounts of AA in the rodent diet do not influence cell-mediated immunity.

Human studies. Two studies of the influence of dietary AA on human immune function have been performed. In the first, AA (1.5 g/d) was included in a low-fat diet (27% energy as fat) consumed for 8 wk by healthy men aged 20–38 yr (35,36). This level of AA did not alter the proliferation of lymphocytes in response to mitogens, NK cell activity, or the DTH response to seven recall antigens (35) and did not alter TNF-α, IL-1β, IL-6, or IL-2 production by mononuclear cells or the in vivo antibody responses to immunization with three strains of influenza virus (36). However, AA did increase production of PGE2 and LTB4 by endotoxin-stimulated mononuclear cells (36). The second study involved supplementing the diet of healthy subjects (men and women) aged 55–75 yr with...
encapsulated AA (~700 mg/d) for 12 wk; there was no effect on NK cell activity (37), mitogen-stimulated lymphocyte proliferation (38), or production of TNF-α, IL-1β, IL-6, IL-2, or IFN-γ by mononuclear cells (38; Thies, F., Newsholme, E.A., and Calder, P.C., unpublished observations). Given that the habitual consumption of AA in free-living Western adults is <300 mg/d, these studies suggest that increasing AA consumption in healthy adults does not have adverse immunological effects. It should be noted, however, that the length of AA administration in these studies was ≤12 wk, and the immunological effects of AA over a longer term are not known.

**α-Linolenic Acid (ALNA; 18:3n-3) and Immune Function**

In *in vitro* studies, ALNA promoted neutrophil adhesion to endothelial cells (11). ALNA inhibited the proliferation of rodent and human lymphocytes *in vitro* (11–16,30–32), decreased the production of IL-2 by mitogen-stimulated rat and human cells (13,14), and inhibited degranulation of cytotoxic T lymphocytes (39). Thus, ALNA has potentially immunosuppressive properties.

**Animal feeding studies.** Compared with feeding a linoleic acid-rich diet, feeding rats linseed oil (100 g/kg diet) for 8 wk decreased superoxide production by peritoneal macrophages in response to phorbol ester but did not affect superoxide production in response to *Listeria monocytogenes* or phagocytosis of *L. monocytogenes* (40). Studies in rodents indicated that linseed oil increased production of TNF by resident macrophages, but had no effect on TNF production by inflammatory macrophages (41–43). High levels of linseed oil in the rodent diet led to decreased lymphocyte proliferation (44,45), NK cell activity (45), and graft vs. host response (45). The precise effect of ALNA on lymphocyte functions appears to depend on the level of linoleic acid and the total PUFA content of the diet (21).

**Human studies.** A high dose of ALNA (15 g/d for 4 wk) decreased IL-1 and TNF production by lipopolysaccharide-stimulated human monocytes (46). Adding linseed oil (providing ~15 g ALNA/d) to a low-fat diet (total fat provided 29% energy) resulted in a significant decrease in human blood lymphocyte proliferation and in the DTH response to seven recall antigens after 6 wk, but circulating antibody levels were unaffected (47). Supplementing the diet of healthy subjects aged 55–75 yr with linseed oil providing 2 g ALNA/d did not significantly affect NK cell activity (37), mitogen-stimulated lymphocyte proliferation (38), or production of TNF-α, IL-1β, IL-6, IL-2, or IFN-γ by mononuclear cells (38; Thies, F., Newsholme, E.A., and Calder, P.C., unpublished observations). Furthermore, supplementing the diet of healthy young men (aged 20–40 yr) with 4.2 g ALNA/d did not alter superoxide production by neutrophils (48). These studies suggest that a moderate increase in ALNA intake by healthy adults does not affect immunity, but that a marked increase in ALNA intake (e.g. 7- to 15-fold) can induce anti-inflammatory and immunosuppressive effects. It is not clear whether these are exerted by ALNA itself or by EPA, a product of ALNA metabolism.

**Long-Chain n-3 PUFA and Immune Function**

Because dietary fish oil leads to decreased PGE2 production (see earlier), it is often stated that it should reverse the effects of PGE2, simply acting as a PGE2 antagonist. If this were so, then fish oil would exert some anti-inflammatory actions (e.g., decreasing fever and vascular permeability) but it would also enhance production of the classic proinflammatory cytokines (TNF, IL-1, and IL-6), enhance production of Th1-type cytokines, increase MHC II expression, lymphocyte proliferation, and NK cell activity, and decrease IgE production.
by B lymphocytes. As described below, many studies, especially those conducted in laboratory animals, have demonstrated that although in some situations fish oil does act as a "PGE₂ antagonist," it often induces effects that are the opposite to those expected on this basis. Thus, the situation is more complex than fish oil simply being a PGE₂ antagonist. PGE₂ is not the sole mediator produced from AA, and the range of mediators produced have varying, sometimes opposite, actions (see earlier). Thus, if fish oil was to act as a "4-series LT antagonist," it would be expected to decrease vascular permeability, leukocyte chemotaxis, neutrophil reactivity, production of proinflammatory and Th1-type cytokines, and NK cell activity. EPA itself will give rise to eicosanoids with varying actions, some augmenting the actions of AA-derived mediators and others antagonizing those actions. In addition, long-chain n-3 PUFA may exert a range of eicosanoid-independent effects, especially upon intracellular signaling mechanisms; these are discussed elsewhere (49,50). Thus, the overall effect of fish oil feeding cannot be predicted solely on the basis of an abrogation of PGE₂-mediated effects.

In vitro studies. Culture with EPA or DHA inhibited superoxide production (51) and phagocytosis (52) by human neutrophils. Incubation with EPA or DHA inhibited cytokine-induced cell surface expression of MHC II (in the mouse these antigens are termed Ia) on mouse peritoneal macrophages (53); DHA was more inhibitory than EPA and other 20-carbon fatty acids and acted by inhibiting the increase in Ia mRNA that occurs after stimulation of macrophages with cytokines (53). Hughes et al. (54) examined the effect of incubation of purified human monocytes with either EPA or DHA upon expression of MHC II, which is termed human leukocyte antigen (HLA); both EPA and DHA decreased the proportion of HLA-DR or -DP positive monocytes after incubation with IFN-γ and decreased the level of expression of these molecules on the monocyte surface (54). In accordance with this, the ability of monocytes cultured with EPA or DHA to present antigen (tetanus toxoid) to autologous lymphocytes was diminished (55). EPA and DHA inhibited production of IL-1β and of TNF-α by human monocytes (28,29) and IL-6 production by rat peritoneal macrophages (56). EPA and DHA inhibited mitogen-stimulation proliferation of rodent and human lymphocyte in culture (12–16,31,32,57–60), decreased the production of IL-2 by rat and human lymphocytes (13,14,59), and decreased human NK cell activity in vitro (59,61,62). Thus, in cell culture, both EPA and DHA exhibit potent anti-inflammatory and immunosuppressive effects.

Animal feeding studies. Feeding fish oil to laboratory animals decreased superoxide and hydrogen peroxide production by macrophages (63–66). Fish oil feeding decreased ex vivo production of TNF-α, IL-1β and IL-6 by rodent macrophages (5,67–69) and monocytes (70). Compared with feeding safflower oil, fish oil feeding resulted in lower peak plasma TNF-α, IL-1β, and IL-6 concentrations after intraperitoneal injection of endotoxin in mice (71). Furthermore, parenteral nutrition supplemented with fish oil decreased serum TNF-α, IL-6, and IL-8 concentrations in burned rats compared with n-6 PUFA–rich parenteral nutrition (72,73). Thus, animal studies reveal significant anti-inflammatory effects of dietary fish oil.

One study reported diminished phagocytosis of Salmonella typhimurium by murine Kupffer cells after feeding fish oil, although this was not associated with a reduced capacity of the cells to kill the bacteria (65). Another study showed that fish oil administered by gastric tube significantly diminished the ability of neonatal rabbits to clear a challenge of Staphylococcus aureus (63). However, there are reports that dietary fish oil does not affect phagocytosis of sheep erythrocytes or yeast particles by murine peritoneal macrophages (66), or of latex beads by porcine alveolar macrophages (74). Feeding fish oil decreased the level of MHC II expression on murine peritoneal macrophages (75) and on rat dendritic cells obtained by cannulation of the thoracic duct (76). Feeding mice an EPA-rich diet for a period of 4–5 wk resulted in diminished ex vivo presentation of antigen (keyhole limpet hemocyanin; KLH) by spleen cells (77). Compared with feeding a low-fat diet or a diet containing 200 g safflower oil/kg, feeding rats a diet containing 200 g fish oil/kg diminished ex vivo KLH presentation by dendritic cells obtained by cannulation of the thoracic duct to KLH-sensitized spleen lymphocytes (76). A recent study reported that dietary fish oil decreased expression of the IFN-γ receptor on murine peritoneal macrophages (78). These studies suggest that dietary fish oil might impair the cell-mediated immune response by decreasing the activity of antigen-presenting cells and by decreasing the sensitivity of macrophages to T lymphocyte–derived cytokines. The effect of dietary fish oil on phagocytosis is unclear.

Animal feeding studies indicate that high levels of fish oil decrease NK cell activity (79–82), cytotoxic T lymphocyte activity (80), expression of the IL-2 receptor on activated lymphocytes (82–84), lymphocyte proliferation (82,83,85–90), and the production of IL-2 (74,90) and IFN-γ (90). Recently, Byleveld et al. (91) showed that feeding mice fish oil significantly impaired the elevation in lung IFN-γ that follows infection with the influenza virus. Dietary fish oil also decreased expression of the IFN-γ receptor on murine splenocytes (78). Dietary fish oil reduced the DTH response in mice compared with n-6 PUFA–rich or olive oil–rich diets (92), whereas addition of either EPA or DHA to the diet of mice consuming a safflower oil diet decreased the DTH response (93); both n-3 PUFA were equally effective. The DTH response to sheep red blood cells in mice was also diminished after tail-vein injections of emulsions of triacylglycerols rich in EPA or DHA (94). Feeding beagle dogs a diet with an n-6/n-3 PUFA ratio of 1.4 resulted in a reduced DTH response to intradermal KLH compared with diets with n-6/n-3 PUFA ratios of 31 or 5.4 (95); the increased n-3 PUFA content was brought about by replacing linoleic acid with EPA plus DHA. A suppressed host vs. graft response was observed in mice fed a diet containing 160 g fish oil/kg compared with those fed a standard chow diet (96); lower levels of fish oil (25, 50,
100 g/kg) did not significantly affect the response. Significantly diminished graft vs. host and host vs. graft responses were observed in rats fed a diet containing 200 g fish oil/kg compared with those fed a low-fat diet or diets containing 200 g coconut, olive, safflower, or evening primrose oil/kg (97). Taken together, these studies suggest that fish oil impairs cell-mediated immunity and induces a shift in T-lymphocyte response away from the Th1-type response, which is involved in both cell-mediated immunity and chronic inflammation. In accordance with this, fish oil enhanced production of IgE to ovalbumin in rats (98).

Animal studies have often used very large amounts of fish oil in the diet, i.e., a diet in which fish oil contributes 20% by weight will mean that EPA plus DHA comprise up to 30% of dietary fatty acids and up to 12% of dietary energy. Recent studies in rats and mice have indicated that relatively low levels of the long-chain n-3 fatty acids (EPA or DHA at a level of 4.4% of total fatty acids or 1.7% of dietary energy) are sufficient to bring about some of the effects of fish oil (99), that dietary EPA and DHA both inhibit lymphocyte proliferation (33,34) and IL-2 production (33), and that dietary EPA, but not DHA, inhibits NK cell activity (34).

**Human studies.** Fish oil, providing >2.3 g EPA plus DHA/d (and in some studies up to 14.5 g/d), decreased chemotaxis of neutrophils (100–104), decreased neutrophil superoxide production (105–107), and decreased neutrophil binding to endothelial cells (100). A recent study providing up to 2.4 g EPA plus DHA/d to healthy subjects for 12 wk did not detect effects on neutrophil chemotaxis or superoxide production (48).

Fish oil, providing 4.5–5.3 g EPA plus DHA/d, decreased chemotaxis of monocytes (101,102,108). Fish oil supplementation decreased zymosan-induced superoxide production by monocytes (109). A more recent study reported no effect of a low dose of n-3 PUFA (0.55 g EPA plus DHA/d for 12 wk) on monocyte chemotaxis (110).

Supplementation of the diet of human volunteers with 1.6 g EPA plus DHA/d for 3 wk resulted in decreased expression of MHC II (HLA-DR, -DQ and -DP) on the surface of blood monocytes (111). Fish oil providing >2.4 g EPA plus DHA/d has been shown to decrease production of TNF (46,108,112,113), IL-1 (46,108,112,113), and IL-6 (112) by mononuclear cells. One other study in which subjects consumed a low-fat diet including oily fish daily (providing 1.2 g EPA plus DHA/d) showed decreased production of TNF, IL-1, and IL-6 (114). In addition, parenteral nutrition supplemented with fish oil decreased serum TNF-α and IL-6 concentrations in patients after major abdominal surgery compared with n-6 PUFA–rich parenteral nutrition (115). In contrast to these observations, a number of studies that provided from 0.55 to 3.4 g EPA plus DHA/d failed to demonstrate an effect of fish oil on production of TNF (24,110,116–118), IL-1 (24,110,116–119), and IL-6 (110,117).

Data from studies investigating the influence of fish oil on human lymphocyte functions are also conflicting. Supplementation of the diet of healthy human volunteers with fish oil providing 2.4 g EPA plus DHA/d resulted in decreased proliferation of lymphocytes from older (aged 51–68 yr) but not young (aged 21–33 yr) women and decreased IL-2 production (112). Molvig et al. (116) reported decreased lymphocyte proliferation after providing 1.7 or 3.4 g EPA plus DHA/d to men, and Gallai et al. (113) reported that 5.2 g EPA plus DHA/d decreased IL-2 and IFN-γ production. Providing 1.2 g EPA plus DHA/d to healthy subjects aged 55–75 yr resulted in decreased NK cell activity (37) and lymphocyte proliferation (38), but did not affect IL-2 or IFN-γ production (38). Finally, inclusion of oily fish providing 1.2 g EPA plus DHA/d in the diet of volunteers consuming a low-fat, low-cholesterol diet decreased lymphocyte proliferation, IL-2 production, and the DTH response to seven recall antigens (114). In contrast to these observations, there are reports of no effect of 3.2 g EPA plus DHA/d on NK cell activity, lymphocyte proliferation, and IL-2 and IFN-γ production (24) and of no effect of 4.6 g EPA plus DHA/d on lymphocyte proliferation and IL-2 production (120).

Taken together these studies indicate that addition of high levels of fish oil to the human diet exerts potent anti-inflammatory effects, particularly decreasing neutrophil and monocyte chemotaxis, superoxide production, and production of proinflammatory cytokines. A high level of dietary fish oil also impairs lymphocyte responses, at least in some studies. Other studies indicated that more modest addition of fish oil to the diet does not affect inflammatory or immune activities. However, there are a large number of studies that fall between the extremes of “modest addition” and “high levels,” and these studies provide conflicting results. It is unclear what the reasons for these discrepancies are, but they might be related to different experimental protocols used, particularly those involving cell preparation, cell culture and cytokine assays, and/or to different subject characteristics (e.g., gender, age, habitual diet) (see Ref. 121 for a discussion).

Some recent studies have examined whether the effects of fish oil are due to EPA or DHA. There was no effect of 3.8 g of either EPA or DHA/d for 7 wk on phagocytosis of opsonized or unopsonized *Escherichia coli* by human monocytes (122). Kelley et al. (123,124) reported the effects in men aged 20–40 yr of including 6 g DHA/d in a low-fat diet (30% energy as fat) for 90 d. There was no effect of DHA on lymphocyte proliferation, serum IgG concentration, or the DTH response to seven recall antigens (123), or on the serum antibody response to immunization with three strains of influenza virus (124). NK cell activity was unaffected at d 55 but was decreased at d 90 (124). Similarly, the production of TNF-α and IL-1β tended to decrease at day 55 but was significantly decreased at day 80 (124). More recently, 750 mg DHA/d was shown not to affect NK cell activity (37), lymphocyte proliferation (38), or the production of TNF-α, IL-1β, IL-6, IL-2, or IFN-γ (38). Thies, F., Newsholme, E.A., and Calder, P.C., unpublished observations) in healthy subjects aged 55–75 yr. Taken together, these data indicate that high levels of DHA (e.g., 6 g/d) can mimic some of the effects of fish oil but that lower levels (e.g., <1 g/d) do not exert any immunological effects in healthy adults.
**EFFECTS OF n-3 PUFA ON INFLAMMATION AND IMMUNITY: IMPLICATIONS AND APPLICATIONS**

As outlined above, a number of animal feeding and human supplementation studies indicate that fish oil can have potent effects on immune function and inflammatory cell responses. Of the two long-chain n-3 PUFA characteristic of fish oil, EPA appears to be more potent than DHA, although high levels of DHA can mimic some of the effects of fish oil. Moderate increases in the intakes of ALNA and AA appear to have little effect on immune function, although high intakes of ALNA have similar effects to fish oil and high intakes of AA have not been studied in humans. The immunological effects of long chain n-3 PUFA are generally termed as anti-inflammatory, and the applications of these effects have been described in terms of chronic inflammatory diseases, allergic inflammation, and acute systemic inflammation in response to trauma. In each of these situations, the benefits of decreased production of 2-series PG (especially PGE_{2}), 4-series LT, and the proinflammatory cytokines, especially TNF-α and IL-1, are evident. The potential detrimental effect on cell-mediated immune responses is often overlooked, although this effect has been demonstrated more easily in animals fed large amounts of fish oil than in humans consuming moderate amounts. In the following sections, the contrasting effects of fish oil on host responses to live pathogens vs. purified endotoxin and the applications to chronic inflammatory diseases and allergic inflammation are described.

**Fish Oil, Infection, and Endotoxemia**

*Animal studies.* The diminished cell-mediated immune responses observed after feeding diets rich in long-chain n-3 PUFA suggest that these fatty acids could impair the host response to infection. Some animal studies support this suggestion. Mice fed a diet containing 200 g fish oil/kg showed lower survival over 15 d (48%) to orally administered *S. typhimurium* than those fed corn oil (62.5%), coconut oil (87.5%), or a low-fat diet (88%) (125); spleens from the fish oil–fed animals contained a greater number of bacteria than those from animals fed the other diets. Similarly, a study of experimental tuberculosis in guinea pigs reported an increased number of bacteria (*Mycobacterium tuberculosis*) in the spleens of fish oil–fed animals, and it was concluded that this represented persistence of the experimental infection (126). Compared with safflower oil, fish oil decreased the clearance of bacteria (inspired *S. aureus*) in neonatal rabbits (63). A diet containing 170 g fish oil/kg decreased survival of mice after an intraperitoneal injection of *L. monocytogenes* compared with feeding 200 g/kg lard, but not compared with feeding 200 g soybean oil/kg, which also resulted in lower survival (127). The spleens from the fish oil–fed mice contained significantly more bacteria than those from the other two groups (127). Recently, fish oil feeding was shown to delay the clearance of influenza virus from the lungs of mice; this was associated with impaired IFN-γ appearance in lung lavage fluid (91). Because the response to microbial and viral infections is predominantly a Th1-mediated response [or at least requires Th1-type cytokines such as IFN-γ (2)], the reduced survival of rodents fed large amounts of fish oil after bacterial challenges confirms that large amounts of fish oil in the diet suppress the Th1 response *in vivo*. In contrast to these observations, some studies show that fish oil feeding does not affect resistance of laboratory rodents to some bacterial (*Pseudomonas aeruginosa*) and viral (murine cytomegalovirus) challenges (128,129). Furthermore, some studies have shown that dietary fish oil enhances survival during some infections. For example, Blok et al. (130) reported increased survival of fish oil–fed mice challenged by intramuscular injection with *Klebsiella pneumoniae*; 90% of fish oil–fed mice survived compared with 30, 40, and 0% in groups fed corn oil, palm oil, or chow, respectively (130). The latter observation is interesting because in human cerebral malaria, an unrestrained Th1 response is detrimental and a Th2 response is helpful (2). The apparent shift away from a Th1- to toward a Th2-type response after fish oil feeding fits with these observations.

In contrast to the detrimental effects of fish oil feeding after challenge with live intact bacteria reported in some studies (see above), intravenous infusion of a 10% (vol/vol) lipid emulsion rich in fish oil into guinea pigs significantly enhanced survival to intraperitoneally injected bacterial endotoxin compared with infusion of a 10% (vol/vol) safflower oil emulsion (131). Furthermore, feeding a diet containing 145 g fish oil/kg to guinea pigs for 6 wk significantly increased survival after an intraperitoneal injection of endotoxin compared with animals fed a diet containing 150 g safflower oil/kg (132). The decreased sensitivity of fish oil–fed animals to endotoxin could be because fish oil decreases the production of the proinflammatory cytokines (see earlier), which are in part the cause of endotoxin-mediated morbidity and mortality. In addition, other studies suggest that fish oil feeding decreases sensitivity to the effects of proinflammatory cytokines. For example, feeding weanling rats a diet containing 100 g fish oil/kg for 8 wk significantly decreased a number of metabolic responses to intraperitoneal TNF-α, i.e., the rises in liver zinc and plasma C3 concentrations, the fall in plasma albumin concentration, and the increases in liver, kidney, and lung protein synthesis rates were all prevented by the fish oil diet (133). Furthermore, fish oil feeding to rats or guinea pigs diminished the pyrogenic (134,135) and anorectic effects (133,136) of IL-1 and TNF-α compared with feeding linoleic acid–containing oils.

It is not entirely clear why fish oil increases susceptibility to pathogens in some studies but not others; this most probably relates to the precise components of the immune response that are required for defense against a particular pathogen, the age of the animals studied, the level of n-3 PUFA in the diet, the mode of administration of the pathogen, and the species.
and strain of animal used. What is apparent, however, is that large amounts of fish oil can impair host defense to live pathogens in vivo (at least in some experimental animal models), and that they protect against the damage induced by pure bacterial endotoxin. These observations agree with the ex vivo measures of immune function. Defense against live bacteria and viruses requires an efficient cell-mediated immune response and this can be impaired by fish oil. In contrast, the damaging effects of purified endotoxin are mediated by macrophage-derived proinflammatory cytokines, whose production is diminished by fish oil feeding.

Human studies. There have been no reports of compromised immunity in humans supplementing their diet with n-3 PUFA. However, most studies of PUFA and immune function have been too small and of too short a duration to identify effects on infection rates; they have also not been designed to investigate rates of infection. However, an epidemic of measles in Greenland triggered by its introduction into the naive population by an infected Danish sailor showed the same characteristics (e.g., expected numbers of cases, complications) as previous epidemics recorded in other naive populations (137). This suggests that the traditional, very n-3 PUFA–rich diet of Greenland Eskimos did not worsen their response to the virus.

Fish Oil and Th-1 Skewed Immunological Diseases

Chronic inflammatory diseases are characterized by a dysregulated Th1-type response and often by an inappropriate production of AA-derived eicosanoids, especially PGE2 and LTB4. The effects of fish oil outlined above suggest that it might have a role in the prevention and therapy of these diseases. Dietary fish oil has been shown to have beneficial clinical, immunological, and biochemical effects in various animal models of human chronic inflammatory diseases. These effects include increased survival and decreased proteinuria and anti-DNA antibodies in mice with autoimmune glomerulonephritis (a model of lupus) (138–141), decreased joint inflammation in rodents with collagen-induced arthritis (142), and less inflammation in rat models of colitis (143,144). The improvements in the model of lupus are associated with ablation of proinflammatory cytokine production and the induction of anti-inflammatory cytokines and antioxidant enzymes (145,146). It was recently reported that both EPA and DHA suppress streptococcal cell wall–induced arthritis in rats, but that EPA was more effective (147); this fits with the more potent effects of EPA than DHA on inflammation and immunity.

There have been a number of clinical trials assessing the benefits of dietary supplementation with fish oil in several inflammatory diseases in humans, including rheumatoid arthritis, Crohn’s disease, ulcerative colitis, psoriasis, lupus, and multiple sclerosis. Trials in some of these diseases are summarized in Table 2. Many of the placebo-controlled, double-blind trials of fish oil in chronic inflammatory diseases reveal significant benefit, including decreased disease activity and a lowered use of anti-inflammatory drugs; the evidence for a beneficial effect of fish oil is strongest in rheumatoid arthritis (Table 2). It was recently observed that n-3 PUFA cause a concentration-dependent decrease in expression and activity of the aggrecanase enzymes that degrade cartilage, in expression of COX 2, but not COX 1, and in TNF-α and IL-1β expression in cultured articular cartilage chondrocytes (156). These observations may explain in part the benefits of fish oil in rheumatoid arthritis. Trials of fish oil supplementation in systemic lupus erythematosus and multiple sclerosis have failed to show significant clinical improvement.

Fish Oil and Th-2 Skewed Immunological Diseases

PGD2, LTC4, LTD4, and LTE4 are produced by the cells that mediate pulmonary inflammation in asthma such as mast cells and are believed to be the major mediators of asthmatic bronchoconstriction (Fig. 9). Although its action as a precursor to LT has highlighted the significance of AA in the etiology of allergic inflammation (Fig. 9), a second link with this fatty acid has been made. This is because PGE2 regulates the activities of macrophages and lymphocytes (see earlier). Of particular relevance in the context of asthma and allergic diseases is the ability of PGE2 to inhibit the production of the Th-1 type cytokines IL-2 and IFN-γ without affecting the production of the Th-2-type cytokines IL-4 and IL-5, and to stimulate B cells to produce IgE. These observations suggest that PGE2 regulates the development of these diseases (Fig. 9). As a result, there has been speculation that the increased intake of linoleic acid, the precursor of AA, that has occurred since the mid-1960s is causally linked to the increased incidence of asthma and allergic diseases over this period (157,158). Thus, a case has been made for increasing the consumption of n-3 fatty acids by patients with allergic diseases (157,158).

There is some epidemiological evidence to support a protective role of long-chain n-3 PUFA in allergic disease (see Ref. 159 for references). These observations make a compelling argument for trials of fish oil in asthma and related diseases, and a number of such trials have been performed. A fish oil–induced reduction in ex vivo LTB4 production by neutrophils from asthmatic patients has been demonstrated (160); most likely, this was accompanied by increased production of 5-series LT. The 5-series LT might be beneficial in asthma because they are unable to elicit an asthmatic response and/or because they block 4-series LT binding to their receptors. Several studies of fish oil supplementation in asthma revealed limited clinical effect, despite significant biochemical changes (e.g., reduced 4-series LT production); details of these studies are discussed elsewhere (see Refs. 159,161). In contrast, some studies have shown significant clinical improvements at least in some patient groups and suggest that this type of approach may be useful in conjunction with other drug- and diet-based therapies (see Ref. 159). A very careful study by Broughton et al. (162) found that low n-3 PUFA ingestion resulted in increased methacholine-induced respiratory distress in asthmatic patients. In contrast, high n-3 PUFA ingestion resulted in an improved response in >40% of subjects; all measures of respiratory function were markedly improved in this group of patients who also showed a markedly elevated appearance of the
TABLE 2
Summary of Clinical Trials of Fish Oil in Chronic Inflammatory Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of double-blind, placebo-controlled studies</th>
<th>Doses of EPA + DHA used (g/d)</th>
<th>Duration (wk)</th>
<th>Key findings</th>
<th>Reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>14</td>
<td>1–7.1</td>
<td>4–52</td>
<td>All studies reported improvements, including reduced duration of morning stiffness, tender or reduced number of swollen joints, reduced joint pain, reduced time to fatigue, and increased grip strength. Twelve studies reported improvement in at least two clinical measures, and five studies reported improvement in at least four clinical measures. Nine studies reported decreased joint tenderness. Three studies reported significant decrease in the use of nonsteroidal anti-inflammatory drugs.</td>
<td>148–152</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>3</td>
<td>2.7–5.1</td>
<td>12–52</td>
<td>Two studies reported no benefit. One study reported a significant decrease in relapses. One other study which used oily fish (100–250 g/d for 2 yr) reported a significant decrease in relapses.</td>
<td>153</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>4</td>
<td>1.8–5.4</td>
<td>12–52</td>
<td>One study reported no benefit (this study used the lowest dose of EPA plus DHA). One study reported a nonsignificant decrease in disease activity and a significant decrease in use of corticosteroids. Two studies reported benefit including improved histologic appearance of the colon, decreased disease activity, weight gain and decreased use of prednisolone. Two other “open” studies reported improved symptoms, improved histologic appearance of the rectal mucosa, and decreased use of prednisolone.</td>
<td>154</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>2</td>
<td>1.8</td>
<td>8–12</td>
<td>One study reported significant improvement in itching, scaling and erythema. One study reported no benefit. Three open studies (providing 10–18 g EPA + DHA/d for 6–8 wk) reported mild-to-moderate (two studies) or moderate-to-excellent (one study) improvements in scaling, itching, lesion thickness, and erythema in the majority of patients.</td>
<td>155</td>
</tr>
</tbody>
</table>

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

EPA-derived 5-series LT in their urine. However, some patients did not respond to the high n-3 PUFA intake. This study suggests that there are patients who respond positively to fish oil intervention and patients who are nonresponders. This suggests that such therapies should be approached cautiously until more is understood about the interaction between fatty acid consumption and disease activity.

DIETARY PUFA AND IMMUNE FUNCTION IN THE NEONATE

None of the studies described above investigated the influence of altering the fatty acid composition of the maternal diet during pregnancy and/or lactation on immune outcomes in the offspring at birth, weaning, or later in life. Only a limited number of such studies have been reported and these are all in animals (163–165).

In the study by Berger et al. (163), female mice were fed before and throughout pregnancy and during lactation diets containing 100 g olive oil, safflower oil, linseed oil, or fish oil/kg. Spleen and thymus weights were determined in the offspring at weaning (d 18). Immune cell functions were determined in the offspring at day 42 but the paper does not indicate the postweaning diet; it is unclear whether it was the same as the maternal diet or was standard chow. At weaning, the offspring of dams fed the olive oil or fish oil diets had smaller spleens than those of dams fed the safflower oil or linseed oil diets. The offspring of dams fed the linseed oil or fish oil diets had smaller thymuses than those of dams fed the olive oil or safflower oil diets. NK cell activity in the offspring at day 42 was decreased by maternal fish oil compared with olive oil and safflower oil. Maternal diet did not affect spleen lymphocyte proliferation or IL-2 production in the offspring.
Rayon et al. (164) fed rats diets containing either 100 g corn or fish oil/kg throughout pregnancy and lactation and then administered live Streptococcus to the 7-d-old pups. The offspring of dams fed corn oil were more susceptible to death (50% mortality over 2 d) than those of dams fed fish oil (25% mortality over 2 d).

The influence of feeding rats diets containing 100 g corn oil, 50 g corn oil plus 50 g coconut oil, or 10 g corn oil plus 90 g coconut oil/kg throughout pregnancy on lymphoid tissue weights and immune cell functions in the offspring was determined (165); the rats were transferred to standard laboratory chow once they had given birth. Spleen lymphocyte proliferation in the offspring at birth was higher if the maternal diet contained 90 g coconut oil. Spleen and thymus weight at weaning increased as the amount of corn oil in the maternal diet increased. Spleen and thymus lymphocyte proliferation at weaning were little affected by maternal diet, but tended to be lowest in the offspring of dams fed the 100 g corn oil/kg diet. Spleen NK cell activity at weaning was highest in the offspring of dams fed the 100 g corn oil/kg diet.

These studies indicate that the nature of the fatty acids in the maternal diet during pregnancy can influence lymphoid tissue development in the offspring, immune cell function in the offspring, and the ability of the offspring to withstand infectious challenges. It is not clear how long the influence of the fatty acid composition of the maternal diet affects the offspring. Nor is it clear how the fatty acid composition of the maternal diet affects the subsequent development of Th1- or Th2-type immunological diseases or subsequent resistance to infection. There is a clear need to explore this area further in appropriate animal models and in human epidemiological and intervention studies.

**GENERAL REMARKS**

Among the fatty acids, it is the n-3 PUFA that possess the most potent immunomodulatory activities, and among the n-3 PUFA, those from fish oil (EPA and DHA) are more biologically potent than ALNA. Components of both natural and acquired immunity, including the production of key inflammatory mediators, can be affected by n-3 PUFA. Animal studies indicate that diets rich in EPA plus DHA are anti-inflammatory and immunosuppressive in vivo, although there have been relatively few good studies in humans. Although some of the effects of n-3 PUFA may be brought about by modulation of the amount and types of eicosanoids made, it is possible that these fatty acids might elicit some of their effects by eicosanoid-independent mechanisms, including actions upon intracellular signaling pathways and transcription factor activity (see Refs. 49,50). Such n-3 PUFA–induced effects may be of use as a therapy for acute and chronic inflammation, and for disorders that involve an inappropriately activated immune response. Moderate levels of AA and DHA do not appear to have any detrimental effects on human immune function, but the effects of these fatty acids have been studied only in healthy adults. The effect of fatty acids during pregnancy upon the maternal immune system and upon that of the infant are not known.

All studies of fatty acids and the human immune system have used adults as subjects, and most studies have used men only or a mixture of men and women. The only study that used women exclusively as subjects was that of Meydani et al. (112); in that study, it was found that the immune system of older women is more sensitive to fish oil than is that of young women. This age-related difference in sensitivity to dietary intervention may explain some of the contradictory observations in the literature [e.g., between (24) and (37, 38)]. It is clear that more needs to be understood about the effect of n-6 and n-3 PUFA on the human immune system and on how variations in age, gender, ethnicity, hormone status, antioxidant status, and genetics influence sensitivity to dietary PUFA. Long-chain n-3 PUFA have been used in a range of diseases characterized by dysregulated Th1- or Th2-type responses and, in a small number of studies, in trauma patients at risk of the systemic inflammatory response syndrome. In these situations, long-chain n-3 PUFA have been beneficial as therapeutic agents. It is not clear what the differential roles of n-6 and n-3 PUFA are in regulating the development of the immune system and how they might affect the likelihood of an individual developing a disease with an immunological component. Clearly, the interactions among PUFA intake, environmental factors, and genetics must be established if we are to fully understand the roles of n-6 and n-3 PUFA in the development and action of the human immune system.

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FATTY ACIDS, INFLAMMATION, AND IMMUNITY


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