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Are Disturbances of ω-6-Fatty Acid Metabolism Involved in the Pathogenesis of Atopic Dermatitis?

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Recent evidence indicates that the primary defect in atopic dermatitis (AD) might concern the maturation and differentiation of T cells which infiltrate the skin or are unable to control T cell infiltration of the skin. Unfortunately, there is no information on thymus hormones, T cell differentiation factors or cytokines during early T cell maturation in atopic infants. One of these factors at fault might involve a deficiency of essential long-chain ω-6-fatty acids and E-type prostaglandins which are important for thymic T cell maturation and thymus hormone action.

Deficiencies of 6-desaturated ω-6-fatty acids have been observed in plasma phospholipids, epidermal and red cell phospholipids of patients with AD, in umbilical cord plasma lecithin of newborn infants with increased cord blood IgE levels, in cord blood T-cells of 'atopy-at-risk' newborn infants, in atopic monocytes, in adipose tissue lipids of patients with AD, in breast milk lipids of mothers with a history of AD, and in breast milk lipids of mothers of infants with AD. Reduced release of arachidonic acid has been measured in atopic monocytes and platelets. Diminished formation of prostaglandin E_2 (PGE_2) has been observed in atopic monocytes under stimulated and unstimulated conditions and in inflamed and non-inflamed atopic epidermis. PGE_2 is able to suppress interleukin 4-induced IgE synthesis of human non-atopic mononuclear cells *in vitro*. We have demonstrated a suppressive effect of PGE_1 and PGE_2 on *in vitro* IgE synthesis of mononuclear blood cells of patients with AD and respiratory allergies. The T-cell differentiating effect of thymus hormones is associated with a high release of E-type prostaglandins, and the antiviral activity of interferons is dependent on normal activity of fatty acid cyclo-oxygenase.

Thus, it is tempting to speculate that metabolic disturbances of long-chain essential fatty acid metabolism in atopic individuals might be linked to an impaired efficacy of thymus hormones in T cell maturation, a diminished PGE-mediated regulation of IgE synthesis and cutaneous T-cell infiltration, and a reduced antiviral activity of interferons. *Key words: Atopic dermatitis; Essential fatty acids; Prostaglandin E; Breast feeding; T-cell maturation.*

Abbreviations: AD = atopic dermatitis; AA = arachidonic acid; LA = *cis*-linoleic acid; GLA = γ-linolenic acid; DGLA = dihomo-γ-linolenic acid; PLP A_2 = phospholipase A_2; PLP C = phospholipase C; PGE = prostaglandin E; cAMP = cyclic 3′,5′-adenosine monophosphate; Ig = immunoglobulin; IgE = immunoglobulin E; PBMC = peripheral blood mononuclear cells; PML = polymorphonuclear leukocytes; ConA = concanavalin A; PHA = phytohemagglutinin; PWM = pokeweed mitogen; IL-4 = interleukin 4; IFN-γ = interferon-γ; IFN-α = interferon-α; BCDF = B cell differentiation factor; MIF = macrophage migration inhibition factor; PITS = prostaglandin-induced T cell derived suppressor; TP-5 = thymopentin; HSF = histamine-induced suppressor factor; EPO = evening primrose seed oil.

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INTRODUCTION

Essential fatty acid deficiency in rodents leads to a scaly dermatitis with a defective epidermal permeability barrier, alterations in cell-mediated immunity with reduced delayed-type hypersensitivity, exaggerated polyclonal immunoglobulin synthesis, increased susceptibility to viral and bacterial infections, and disturbances in thymus development (1–4). Intriguingly, most patients with atopic dermatitis (AD) have a dry skin with increased transepidermal water loss, reveal a reduced capacity to manifest delayed-type hypersensitivity, produce increased amounts of immunoglobulin E (IgE), and exhibit disturbances in essential ω-6-fatty acid metabolism (5–7).

Disturbed essential fatty acid metabolism in atopic dermatitis

In 1937, Brown & Hansen detected depressed serum levels of AA in patients with AD and suggested defective functioning of ω-6-fatty acid metabolism as a possible cause of AD (8). Recent studies confirmed that the essential ω-6-fatty acid *cis*-linoleic acid (LA) is not regularly metabolized in patients with AD (9–11) (Fig. 1). Plasma phospholipids reveal depressed levels of γ-linolenic acid (GLA), dihomo-γ-linolenic acid (DGLA, the precursor of prostaglandin E_1 (PGE_1), and AA, the precursor of prostaglandin E_2 (PGE_2), whereas the levels of LA are even higher than normal. Depressed levels of DGLA and AA were recently detected in red cell phospholipids and epidermal phospholipids of AD patients (12, 13), in adipose tissue lipids of patients with AD (14), and in cord blood T-lymphocytes of 'atopy-at-risk' newborn infants (15). Elevated levels of LA and depressed levels of GLA, DGLA, and AA have been observed in breast milk lipids of mothers with a history of AD (16), and in breast milk lipids of mothers of infants with AD (17), supporting the view of defective functioning of ω-6-fatty acid metabolism in AD. A striking correlation has been shown between elevated levels of LA in umbilical cord serum lecithin and elevated cord serum IgE (10), a well-recognized predictor for the development of atopic disease (18). Accumulating evidence suggests that a deficiency of long-chain ω-6-fatty acids in atopic subjects is

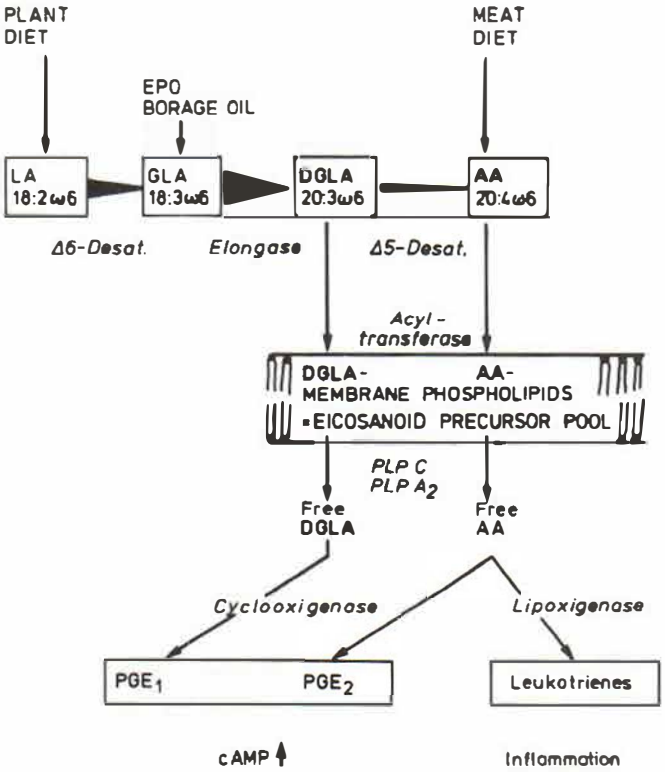

Fig. 1. Metabolic pathway of dietary essential ω-6-fatty acids. The rate-limiting-enzyme of ω-6-fatty acid metabolism, the Δ6-desaturase, has been suggested to be deficient in patients with atopy [9]. Under physiological conditions there is a reduced capacity for Δ5-desaturation in man. In patients with AD reduced levels of long-chain ω-6-fatty acids in membrane phospholipids which comprise the eicosanoid precursor pool have been observed. Oral administration of evening primrose (EPO) or borage oil increases the formation of prostaglandins of the 1-series – but not of leukotrienes, whereas meat-derived arachidonic acid gives rise to prostaglandins of the 2-series and also the leukotrienes.

related to diminished formation of E-type prostaglandins which are potent cAMP-mediated activators of suppressor T cell function (19).

Altered prostaglandin E-mediated regulation of IgE synthesis

T cell-mediated immunity, especially suppressor T cell numbers and function, are depressed in atopic subjects (5, 20). Pathologically increased *de novo* IgE synthesis by cultured atopic peripheral blood mononuclear cells (PBMC) could be suppressed by adding T cells, especially suppressor T cells, from non-atopic donors (21–23), whereas depletion of CD8+ suppressor/cytotoxic T cells resulted in a further increase in *in vitro* IgE secretion (24). The cAMP-elevating agents, dibutyryl-cAMP, isoproterenol, and theophyllin, were found to suppress the spontaneous *in vitro* IgE synthesis of PBMC from patients with AD (25).

IgE synthesis results from a complex interaction between T cells, B cells, and monocytes, under the control of T cell-derived and monocyte-derived lymphokines (26, 27). Monocytes are capable of inhibiting lymphocyte proliferation by mechanisms that involve PGE synthesis (28, 29). Monocyte-macrophages are the major PGE-secreting cells of human peripheral blood (30) (Fig. 2). Atopic monocytes, however,

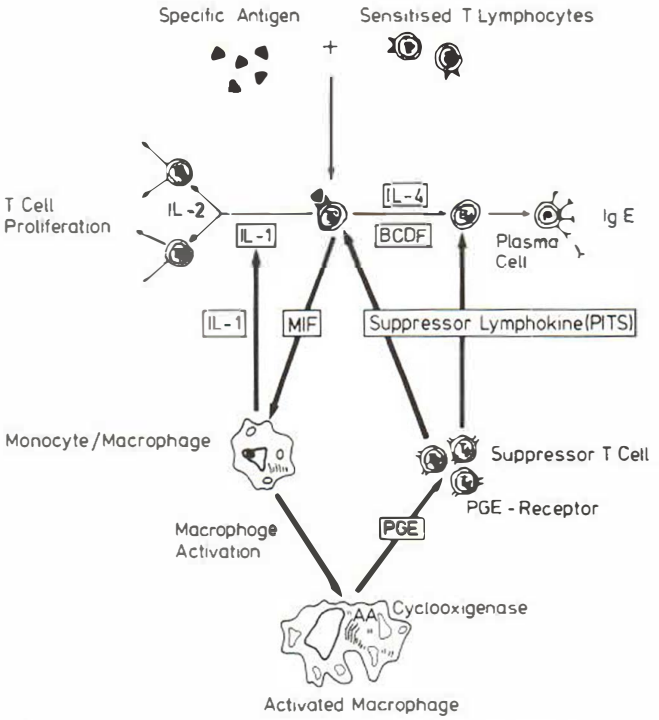

Fig. 2. Deficient monocyte-PGE-mediated 'feedback' inhibition of T cell proliferation and IL-4-induced IgE production in atopy due to diminished arachidonic acid content and altered PGE formation of atopic monocytes, reduced numbers of PGE_2-receptors of atopic T cells, and reduced numbers of suppressor T cells.

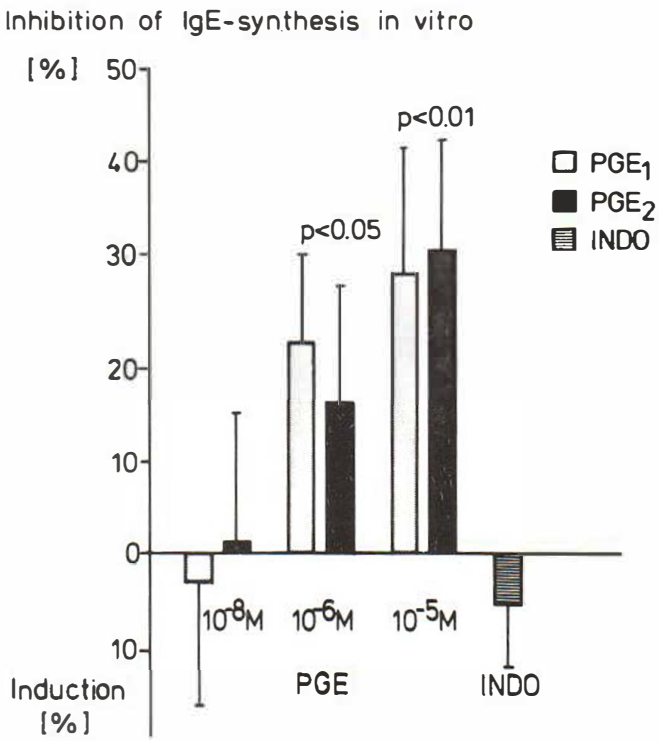

Fig. 3. PGE-mediated inhibition of spontaneous *in vitro* IgE synthesis of atopic peripheral blood mononuclear cells (PBMC) from 15 adult patients with severe AD and respiratory allergies (serum IgE > 1000 IU/ml) in comparison with untreated PBMC cultures (6 days, 37°C) or addition of 3.6×10^{-5} M indomethacin (*INDO*). With permission of [7].

not only contain less of the PGE_2-precursor AA (11), but when stimulated with histamine-induced suppressor factor (HSF) respond with a reduced output of PGE_2 in comparison with non-atopic monocytes (31). Under unstimulated conditions, atopic monocytes produced significantly less cyclo-oxygenase products than did normal monocytes (32). Binding of IgE to low affinity receptors for IgE ($Fc\varepsilon R_2$ = CD23) on monocytes activates the effector function of these cells and induces the release of eicosanoids and other monokines (27). Increased numbers of circulating CD23+ monocytes have been observed in atopic patients (33). Moreover, interleukin 4 (IL-4) and γ-interferon (IFN-γ) induce $Fc\varepsilon R_2$/CD23 on human epidermal Langerhans cells (34), which may play a role in the pathogenesis of AD (35).

Pène and co-workers recently demonstrated that normal IL-4-induced IgE synthesis was dependent on CD4+ T cells and monocytes and was blocked by IFN-γ, IFN-α, and PGE_2 (36). These mediators also inhibited IL-4-induced CD23 expression and subsequent release of soluble CD23. These observations imply that dysregulation of AA content, release and metabolism as well as PGE formation of atopic monocytes might play an important role in the disturbed immunoregulation of the atopic IgE/$Fc\varepsilon R_2$ system. The question arose as to whether deficiencies in PGE signal transduction might be involved in insufficient down-regulation of IgE synthesis. Fig. 3 demonstrates that spontaneous *in vitro* IgE synthesis of PBMC of patients with severe AD and respiratory allergies (total serum IgE > 1000 U/ml) could be significantly suppressed by adding 10^{-6} and 10^{-5} M PGE_1 or PGE_2, whereas addition of the cyclo-oxygenase inhibitor indomethacin resulted in a further increase in pathologically elevated IgE secretion (7). This experiment points to a physiological role of PGE-mediated signals for the down-regulation of IgE synthesis. The further increase in IgE synthesis after adding indomethacin might explain the frequently observed type I-allergy-like intolerance reactions of atopic persons after ingesting cyclo-oxygenase inhibitors.

The addition of 10^{-7} and 10^{-6} M PGE_2 to PBMC from healthy donors resulted in a 50% and 67% inhibition of IL-4 induced IgE production, respectively (37). Suppression of IgE synthesis was also observed in the presence of relative high monocyte concentrations (37). These observations emphasize that PGE is a physiologically important regulator of human IgE synthesis. In comparison with non-atopic PBMC, atopic PBMC appear to be less sensitive to PGE-mediated inhibitory signals for IgE synthesis.

Prostaglandin E_2-receptor deficiency on atopic T lymphocytes

Normal human lymphocytes exhibit high affinity binding sites for PGE_1 and PGE_2 (38, 39). The cAMP-response to PGE_2 is not equally distributed among lymphocytes (40). Intriguingly, human T lymphocytes exhibiting high affinity binding sites for PGE_2 had a strong suppressor effect on pokeweed mitogen (PWM)-driven B-cell maturation into immunoglobulin (Ig)-containing cells (41). The majority of these PGE_2-binding T lymphocytes expressed the suppressor T cell marker CD8. However, atopic helper- and suppressor T cells revealed decreased sensitivity to PGE_2 (42). This PGE-hyporesponsiveness could recently be explained by a reduction of PGE_2-receptors on atopic T lymphocytes (372±61 PGE_2-receptors/T cell vs. 1004±118 PGE_2-receptors on non-atopic T cells) (43). The addition of PGE_2 (10^{-12} to 10^{-6} M) to cultures of non-atopic T cells stimulated with phytohemagglutinin (PHA) resulted in a dose-dependent suppression of T cell proliferation, whereas the inhibitory effect of PGE_2 on atopic T cells was significantly less (43).

Prostaglandin E tunes T- and B-cell responses

PGE_2 at concentrations of approximately 10^{-8} to 10^{-5} M inhibit a variety of lymphocyte functions including the effector function of cytotoxic T lymphocytes, natural killer cells, E-rosetting, and proliferation to the mitogens PHA and concanavalin A (44–46). PGE_2 inhibits antigen- and mitogen-induced production of interleukin-2 (IL-2) (47, 48), the expression of IL-2-receptors on human T cells (49), and the IL-2-transduction pathway in murine T cell clones (50). E-series prostaglandins are potent growth inhibitors for some B cell lymphomas (51). PGE_2 at physiologically relevant concentrations inhibited the production of B cell differentiation factor from mitogen-stimulated T cells and suppressed the generation of Ig-secreting cells in a dose-dependent manner (52). Fischer and co-workers (41) added PGE_2-receptor-positive and PGE_2-receptor-negative T cell populations to human autologous PBMC that were stimulated with PWM to mature into Ig-containing cells. PGE_2-receptor-positive T cells did exert a strong suppressor effect on PWM-driven B cell maturation into IgM-, IgG-, and IgA-containing cells.

The capacity of PGE_2 to inhibit lymphocyte proliferation may be exerted either directly or by activating suppressor T cells. One pathway where PGE_1 acts involves the stimulation of a glasswool adherent suppressor T-cell which releases a suppressor lymphokine, termed the prostaglandin-induced T-cell derived suppressor (PITS) (53). There are other examples which clearly demonstrate that products of AA metabolism are important to the activity of antigen-nonspecific suppressor lymphokines (54). The ability of histamine-induced suppressor factor (HSF) to suppress [^{3}H] thymidine incorporation by lymphocytes stimulated by T-cell mitogens is blocked by indomethacin. Monocytes, after stimulation with HSF, secrete PGEs which activate suppressor T cells which inhibit [^{3}H]-thymidine incorporation by mitogen-stimulated T cells (31, 54). PGE_1 and PGE_2 have been shown to stimulate the M1–A5 cell line, isolated from the spleen of a tumour-bearing mouse, to secrete a suppressor cell-inducing factor (55).

Taken together, evidence has accumulated that monocyte/PGE-mediated suppressor T cell activation plays an important role for the immunoregulation of T- and B-cell responses (19, 56). The decreased conversion of LA to the PGE precursors GLA, DGLA, and AA, the diminished PGE_2 formation of HSF-stimulated atopic monocytes, and the receptor-dependent PGE-hyporesponsiveness of atopic lymphocytes may lead to disturbances of PGE-mediated immunoregulation in atopy.

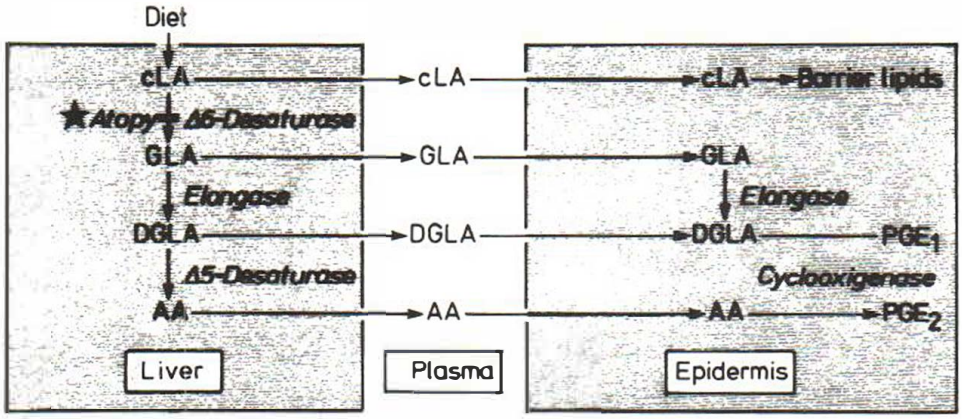

Fig. 4. Metabolic interactions between hepatic, plasma, and epidermal ω-6-fatty acid metabolism. GLA and AA are essential for the epidermis due to the physiological absence of epidermal Δ6- and Δ5-desaturase activities. A deficiency of hepatic Δ6-desaturase activity leads to a reduction of epidermal levels of PGE-precursor fatty acids.

Relative deficiency of E-type prostaglandins in atopic skin

The immunopathology of AD which represents a form of delayed hypersensitivity is characterized by T cells of the helper/inducer phenotype, monocytes, but only occasional CD8+ T cells of the suppressor/cytotoxic phenotype (20, 57). In inflamed skin of patients with AD, no elevation of PGE_2 could be measured (58), indicating a relative deficiency of this mediator. Non-involved skin of patients with AD exhibited a deficiency of PGE_2 as well as 12- and 15-hydroxyeicosatetraenoic acid (59). The deficiency of PGE_2 in skin of patients with AD can now be attributed to an impaired systemic supply of Δ6-desaturase products and the physiological inability of mammalian epidermis for Δ6- and Δ5-desaturation (60, 61) (Fig. 4). Thus, GLA and AA are essential for the human epidermis. The improvement of AD by oral and topical administration of GLA-rich evening primrose oil (EPO) (62–64) appears to be related to an increase in PGE-precursor fatty acids, DGLA and AA, and PGE in plasma (9, 62). Oral administration of GLA-rich borage oil to guinea pigs resulted in increased epidermal levels of PGE_1 and PGE_2 (65), and the generation of other anti-inflammatory epidermal mediators such as 15-hydroxy-DGLA (66, 67). It has been shown that PGE_1 and PGE_2 inhibit leukotriene B_4 release of activated rat and human polymorphonuclear neutrophils (PMN) in a dose-related manner (68). This action is associated with elevated levels of cAMP. The inhibitory activity of PGE appears to be PGE-receptor-dependent. Moreover, O_2^- release of PMN is suppressed by PGE_1 and PGE_2 in a dose-dependent manner (68). The anti-inflammatory effect of GLA-rich plant oils might result from a modulation of the eicosanoid precursor pools. It is known that GLA-derived DGLA is the precursor of monoenoic prostaglandins, but not for the leukotrienes, whereas AA is the precursor for dienoic prostaglandins and the leukotrienes (69, 70). E-type prostaglandins, which raise intracellular cAMP levels, are potent inhibitors of mast cell degranulation (71). Ultraviolet irradiation which raises cutaneous PGE levels (72, 73) is known to suppress mast cell-mediated whealing in human skin (74). Thus, immunological, biochemical, and clinical evidence suggests that alterations of PGE-mediated feedback systems in AD might contribute to 1) an insufficient unspecific down-regulation of IgE synthesis, 2) an increased release and expression of CD23, 3) an enhanced cutaneous T cell proliferation as well as an increased releasability of mast cell-derived mediators.

Essential fatty acids, E-type prostaglandins and thymocyte differentiation

There is accumulating evidence that deficiencies in PGE-mediated signal transmission might also be responsible for impaired suppressor T cell differentiation and T cell maturation as well as depressed cell-mediated immunity. PGE enhances the proliferative response of immature thymocytes (75). Anti-PGE antibodies inhibit *in vivo* development of cell-mediated immunity (76). From *in vitro* experiments it is concluded that cAMP is the intracellular mediator for regular differentiation of prothymocytes to thymocytes (77). The cAMP inducer PGE_1 is present in the thymus and reveals thymus hormone-like activities in promoting T cell maturation and function (78). Lymphocyte subpopulations from mice exhibit different responsiveness to 10^{-6} M PGE_1 that correlated with their anatomic origin: Thymic lymphocytes were most responsive (36-fold increase in cAMP levels), followed by splenic lymphoid cells (sixfold), lymph node cells (threefold), and peripheral blood lymphocytes (1.2-fold) (78). These observations indicate that there is an increased sensitivity of T lymphocytes for PGEs during their early maturation and differentiation process in the thymus.

The tissue content of the long-chain polyunsaturated fatty acids is affected by the dietary essential fatty acids (69). The level of PGE_2 synthesis of rat thymus homogenates is clearly dependent on the amount of polyunsaturated essential fatty acids fed to the animals (3). The availability and affinity of essential fatty acids for incorporation into the eicosanoid precursor pools is of great importance for prostaglandin production (69, 70).

Recent evidence suggests that human thymic epithelial cells and thymic macrophages produce substantial amounts of PGEs (79, 80). Moreover, it has been demonstrated that thymosin induces an early and dose-dependent release of high concentrations of PGE_2 by lymphocytes collected from thymectomized mice (81). The release of PGE_2 was associated with the induction of theta-antigen and was totally inhibited by indomethacin. Garaci et al. (82) could demonstrate that a synthetic long-acting analog of PGE_2, 16,16-dimethylprostaglandin E_2-methylester, was able to induce *in vivo* theta anti-

gen expression on spleen cells of adult thymectomized mice. This PGE_2 analog could mimic the effects of thymic hormone with respect to induction of theta antigen. In agreement with these findings it has been shown that the incubation of fetal mouse thymic stem cells with PGE_1 had a maturation effect and increased the proportion of Thy-1-positive cells (83).

Thus, it is likely that the PGE-precursor deficiency of atopic monocytes and the PGE_2-receptor deficiency on atopic lymphocytes will affect thymic differentiation and maturation of PGE-binding suppressor T cells (84). Support for this suggestion comes from fetal mice thymic organ cultures which were capable of metabolizing AA to PGE_2. The addition of indomethacin inhibited the expression of Lyt-2, the surface marker characterizing mouse suppressor T cells (85).

Essential fatty acids and anti-viral activity

Strannegård and co-workers (86) suggested that the mechanism underlying the increased susceptibility to viral infections in patients with AD may be related to immunological aberrations that are secondary to a basic abnormality in the essential fatty acid or cAMP metabolism: "There is the possibility that an abnormality of enzymes of essential fatty acid metabolism constitute the genetic basis for the immunological defect in AD". Intriguingly, Pottathil and co-workers (87) demonstrated that fatty acid cyclo-oxigenase (prostaglandin synthase, E.C. 1.14.99.1), which is necessary for prostaglandin biosynthesis from AA, is required for the optimum expression of interferon-induced antiviral state. Their observations have been confirmed with a clone of L1210 mouse leukemia cells selected for resistance to both the antiviral and anticellular properties of mouse interferon. This cell line was devoid of fatty acid cyclo-oxygenase activity (88). On the other hand, it is known that virally transformed cells in culture delete the expression of Δ6-desaturase, the rate-limiting enzyme of essential fatty acid metabolism (89).

Long-chain essential fatty acids and the type of infant feeding

The basic defect of essential fatty acid metabolism in patients with AD is not known. The shortage of long-chain essential fatty acids and the relative increase in linoleic acid are at present best explained by an impaired activity of the rate-limiting enzyme of essential fatty acid metabolism, the Δ6-desaturase (9, 12). Further possibilities are an increased activity of phospholipase A_2 (13) or an increased activity of phosphoinositide specific phospholipase C in mononuclear leukocytes of patients with AD (90). There is no information on the activity of essential fatty acid acyltransferase activities and the incorporation of PGE precursor fatty acids into various lipid compartments.

According to Thestrup-Pedersen (91) AD can be considered to be due to an inborn error of the maturation of epithelial tissue. This maturation is essential for both the appearance of normal skin and for the regular maturation of the cell-mediated immune system. For the optimal function and integrity of both tissues, essential fatty acids are of great biological importance (3, 92). The disappearance of AD in childhood and the reduction in severity observed in many patients after the first years of life might be explained by a retarded maturation process. Assuming that the long-chain essential ω-6-fatty acids are the missing maturation factor for the immune system in the atopic infant, the preferential requirement and incorporation of long-chain essential fatty acids into brain lipids during rapid brain growth after birth might result in a relative deficiency of these factors in other tissues, such as the thymus epithelium and the skin. Another explanation for the increased incidence of AD in industrialized countries might be a relative deficiency of long-chain essential fatty acids due to an acceleration in general growth. There are other 'intrinsic' changes in recent decades which might be involved in the increased incidence of AD. We do not know whether several years' hormonal contraception preceding pregnancy and lactation might have altered the metabolism and body stores of essential fatty acids, because Δ6- and Δ5-desaturase activities are modified by hormonal changes (93).

The progress in our understanding of the role of essential fatty acids and E-type prostaglandins for the normal development and function of cell-mediated immunity is supported by the observation that prolonged breast feeding protects against the manifestation of atopy later in life (94, 95). Human colostrum and mature human milk, in contrast to cow-milk based formula, are rich in GLA, DGLA, AA, and prostaglandins (96). In infants with low numbers of circulating T cells, IgE levels in the serum were found to be elevated when those children were bottle-fed early in life, whereas breast-fed infants with low T-cell counts had IgE levels similar to those in infants with normal T cell counts who were breast- or bottle-fed (97). Tainio (98) has studied the effects of age, type of feeding, atopic heredity and atopy on the distribution of lymphocyte subsets in infants. He showed that breast-fed infants had relatively more suppressor (CD8) cells than infants receiving formula. Available formulas contain relatively small amounts of long-chain ω-6-fatty acids.

The observed induction of PGE release by thymus hormones and the thymic hormone-mimicing effects of E-type prostaglandins might indicate that the optimal availability of PGE precursors and the formation of sufficient amounts of E-type prostaglandins might be necessary for the optimal efficacy of thymus hormones for regular T cell maturation. In this regard it is most intriguing that treatment of AD patients with thymopentin (TP-5) tends to normalize the suppressor cell phenotype deficiency (99) and reduces the clinical severity of AD (100). Further support comes from *in vitro* experiments, demonstrating that thymosin was able to induce suppressor T lymphocytes (101).

The recent finding that breast milk of mothers with AD (16) and of mothers of infants with AD (17) contains reduced concentrations of essential PGE precursor fatty acids, is consistent with epidemiologic studies on the transmission of atopy. Children of atopic mothers exhibit atopic manifestations more often than do children of atopic fathers (44% vs. 25.5%) (102). Mothers with respiratory atopy more often have atopic children (26%) than do fathers with respiratory atopy (13%) (103). These findings might explain the conflicting results obtained from studies designed to evaluate the role of breast feeding in preventing the manifestation of atopic disease (104). Atopic mothers who lack long-chain polyunsat-

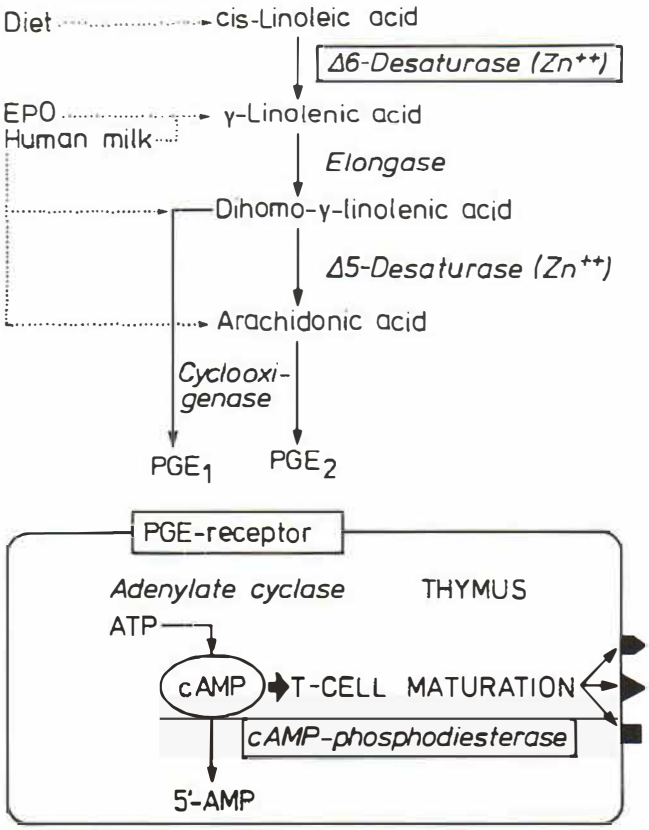

Fig. 5. The metabolism of ω-6-fatty acids and E-type prostaglandins (*PGE*) and their suggested role for normal T cell maturation in the thymus. Breast milk- or evening primrose oil (EPO)-derived long-chain ω-6-fatty acids might stimulate T-cell maturation by induction of PGE- and cAMP-levels.

urated ω-6-fatty acids in their breast milk might be unable to confer protection to their infants at genetic risk for atopy (105).

Unlike infant formula, breast milk is an important source of long-chain polyunsaturated fatty acids for the developing infant. Without breast milk the infant has to rely on its own ability to synthesize long-chain polyunsaturated fatty acids from the precursors in infant formula, namely LA and α-linoleic acid. There is recent evidence that this ability is partially restricted. It has been shown that membrane phospholipids from crythrocytes of infants fed infant formula containing LA and α-linoleic acid but no long-chain polyunsaturated fatty acids have fewer long-chain polyunsaturated fatty acids than infants fed breast milk (106, 107). Gibson & Rassias (108) studied the effect of different dietary supplements containing LA *or* LA and GLA on the plasma and breast milk fatty acid composition in lactating women. Despite the fact that both safflower and linseed oil contained high percentages of LA, no increase in the long-chain metabolites of LA was seen in either plasma or breast milk. On the other hand, supplementation with GLA-rich EPO or blackcurrant seed oil resulted in increased concentration of long-chain ω-6-fatty acids in plasma and breast milk (108). It has been calculated that daily 105 g egg yolk or 168 g chicken liver has to be given to a 6-month-old bottle-fed infant weighing 7 kg in order to provide the equivalent quantity of long-chain ω-6-fatty acids administered by daily breast feeding (108). These observations are of great importance for the atopic situation, in which deficiencies of long-chain ω-6-fatty acids have been measured in various tissues. The atopic infant appears to be strongly dependent on the availability of long-chain ω-6-fatty acids which can best be provided by breast feeding.

These new insights may offer a rational approach for the prevention of AD by adequate supplementation of the atopic woman during pregnancy and lactation as well as of her newborn infant, with long-chain ω-6-fatty acids (105) (Fig. 5).

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REFERENCES

1. Burr GO, Burr MM. A new deficiency disease produced by the rigid exclusion of fat from the diet. J Biol Chem 1929; 82: 345–367.
2. Holman RT. Essential fatty acid deficiency. Prog Lipid Res 1971; 9: 275–348.
3. Johnston PV. Dietary fat, eicosanoids, and immunity. Adv Lipid Res 1985; 21: 103–141.
4. Mertin J, Stackpoole A, Shumay S. Nutrition and immunity: the immunoregulatory effect of n-6 essential fatty acids is mediated through prostaglandin E. Int Arch Allergy Appl Immunol 1985: 77; 390–395.
5. Rajka G. Essential aspects of atopic dermatitis. Berlin, Heidelberg, New York, Springer 1989.
6. Brown MA, Hanifin JM. Atopic dermatitis. Current Opinion in Immunology 1990; 2: 531–534.
7. Melnik BC, Plewig G, Tschung T. Disturbances of essential fatty acid- and prostaglandin E-mediated immunoregulation in atopy. Prostalglandins Leukotrienes and Essential Fatty Acids 1991; 42: 125–130.
8. Brown WR, Hansen AE. Arachidonic and linoleic acid of the serum in normal and eczematous human subjects. Proc Soc Exp Biol Med 1937; 36: 113–117.
9. Manku MS, Horrobin DF, Morse N, Kyte V, Jenkins K, Wright S, Burton JL. Reduced levels of prostaglandin precursors in the blood of atopic patients: defective delta-6-desaturase function as a biochemical basis for atopy. Prostagl Leukot Med 1982; 9: 615–628.
10. Strannegård I-L, Svennerholm L, Strannegård O. Essential fatty acids in serum lecithin of children with atopic dermatitis and in umbilical cord serum of infants with high or low IgE levels. Int Arch Allergy Appl Immunol 1987; 82: 422–423.
11. Rocklin RE, Thistle L, Gallant L, Manku MS, Horrobin D. Altered arachidonic acid content in polymorphonuclear and mononuclear cells from patients with allergic rhinitis and/or asthma. Lipids 1986; 21: 17–20.
12. Oliwiecki S, Burton JL, Elles K, Horrobin DF. Levels of essential and other fatty acids in plasma and red cell phospholipids from normal controls and patients with atopic eczema. Acta Derm Venereol (Stockh) 1991; 71: 224–228.
13. Schäfer L, Kragballe K. Abnormalities in epidermal lipid metabolism in patients with atopic dermatitis. J Invest Dermatol 1991; 96: 10–15.
14. Wright S, Sanders TAB. Adipose tissue essential fatty acid composition in atopic dermatitis, Symposium Dermatology in the Year 2000, London, May 22–25, 1990.
15. Galli E, Picardo M, De Luca C, Nardi S, Anastasio E, Ioppi M, Businco L. Essential fatty acids in cord blood lymphocytes of infants "at risk" for atopy. Pediatric Res 1989; 26: 519.
16. Wright S. Essential fatty acids and atopic eczema: biochemical and immunological studies. In: Horrobin DF, ed. Omega-6 es-

sential fatty acids: Pathophysiology and roles in clinical medicine. New York: Alan R Liss 1990; 55–65.
17. Wright S, Bolton C. Breast milk fatty acids in mothers of children with atopic eczema. Br J Nutr 1989; 62: 693–697.
18. Croner S, Kjellman NI, Ericksson B, Roth A. IgE screening in 1,701 newborn infants and the development of atopic disease during infancy. Arch Dis Childh 1982; 57: 364–368.
19. Bray MA. Prostaglandins and leukotrienes: Fine tuning the immune response, ISI Atlas of Science: Pharmacology 1987; 101–105.
20. Sustiel A, Rocklin R. T cell responses in allergic rhinitis, asthma and atopic dermatitis. Clin Exp Allergy 1989; 19: 11–18.
21. Geha RS, Reinherz E, Leung D, McKee KT Jr, Schlossman S, Rosen FS. Deficiency of suppressor T cells in the hyperimmunoglobulin E syndrome. J Clin Invest 1981; 68: 783–791.
22. Hemady Z, Blomberg F, Gellis S, Rocklin RE. IgE production in vitro by human blood mononuclear cells: a comparison between atopic and nonatopic subjects. J Allergy Clin Immunol 1983; 71: 324–330.
23. Hemady Z, Gellis S, Chambers M, Rocklin RE. Abnormal regulation of in vitro IgE synthesis by T cells obtained from patients with atopic dermatitis. Clin Immunol Immunopathol 1985; 35: 156–168.
24. Thomas P, Senner H, Rieber P, Ring J. In vitro IgE-secretion in atopic eczema: influence of allergens and mitogens and role of CD8 T cell subpopulation. Acta Derm Venereol (Stockh) 1989; Suppl 144: 110–114.
25. Strannegård Ö, Strannegård I-L. Effect of cyclic AMP-elevating agents on human spontaneous IgE synthesis in vitro. Int Archs Allergy appl Immun 1984; 74: 9–14.
26. Romagnani S. Regulation and deregulation of human IgE synthesis. Immunology today 1990; 11: 316–321.
27. Vercelli D, Geha RS. Regulation of IgE synthesis in humans. J Clin Immunol 1989; 9: 75–83.
28. Goodwin JS, Ceuppens J. Regulation of the immune response by prostaglandins. J Clin Immunol 1983; 3: 295–315.
29. Stenson WF, Parker CW. Prostaglandins and the immune response. In: Lee O, ed. Prostaglandins. Amsterdam: Elsevier/North-Holland, 1982; 39–90.
30. Gordon D, Bray MA, Morley J. Control of lymphokine secretion by prostaglandins. Nature 1976; 262: 401–402.
31. Matloff SM, Kiselis IK, Rocklin RE. Reduced production of histamine-induced suppressor factor (HSF) by atopic mononuclear cells and decreased prostaglandin E_2 output by HSF-stimulated atopic monocytes. J Allergy Clin Immunol 1983; 72: 359–364.
32. Lans DM, Rocklin RE. Dysregulation of archidonic acid release and metabolism by atopic mononuclear cells. Clin Exp Allergy 1989; 19: 37–44.
33. Spiegelberg HL. Structure and function of Fc receptors for IgE on lymphocytes, monocytes and macrophages. Adv Immunol 1984; 35: 61–88.
34. Bieber T, Rieger A, Neuchrist C, Prinz JC, Rieber EP, Botz-Nitulescu G, Scheiner O, Kraft D, Ring J, Stingl G. Induction of $Fc\varepsilon R_2$/CD23 on human epidermal Langerhans cells by human recombinant interleukin 4 and γ interferon. J Exp Med 1989; 170: 309–314.
35. Bruynzeel-Koomen C. IgE on Langerhans cells: new insights into the pathogenesis of atopic dermatitis. Dermatologica 1986; 172: 199–205.
36. Pène J, Chrétien I, Rousset F, Brière F, Bonnefoy JY, de Vries JE. Modulation of IL-4-induced human IgE production in vitro by IFN-γ and IL-5: the role of soluble CD23 (s-CD23). J Cell Biochem 1989; 39: 253–264.
37. Pène J, Rousset F, Brière F, Chrétien I, Bonnefoy J-Y, Spits H, Yokota T, Arai N, Arai K-I, Banchereau J, de Vries JE. IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferons γ and α and prostaglandin E_2. Proc Natl Acad Sci 1988; 85: 6880–6884.
38. Goodwin JS, Wilk A, Lewis M, Bankhurst AD, Williams RC Jr. High-affinity binding sites for prostaglandin E on human lymphoctes. Cell Immunol 1979; 43: 150–159.
39. Plaut M. Lymphocyte hormone receptors. Ann Rev Immunol 1987; 5: 621–669.
40. Goodwin JS, Kaszubowski PA, Williams RC Jr. Cyclic adenosine monophosphate response to prostaglandin E_2 on subpopulations of human lymphocytes. J Exp Med 1979; 150: 1260–1264.
41. Fischer A, Le Deist F, Durandy A, Griscelli C. Separation of a population of human T lymphocytes that bind prostaglandin E_2 and exert a suppressor activity. J Immunol 1985; 134: 815–819.
42. Rocklin RE, Thistle L, Audera C. Decreased sensitivity of atopic mononuclear cells to prostaglandin E_2 (PGE_2) and prostaglandin D_2 (PGD_2). J Immunol 1985; 135: 2033–2039.
43. Rocklin RE, Thistle L. Reduced prostaglandin E_2 (PGE_2) receptors on atopic T lymphocytes. Cell Immunol 1986; 99: 294–299.
44. Baker PE, Fahey JV, Munck A. Prostaglandin inhibition of T-cell proliferation is mediated at two levels. Cell Immunol 1981; 61: 52–61.
45. Fischer A, Durandy A, Griscelli C. Role of prostaglandin E_2 in the induction of nonspecific T lymphocyte suppressor activity. J Immunol 1981; 126: 1452–1455.
46. Stobo JD, Kennedy MS, Goldyne ME. Prostaglandin E modulation of the mitogenic response of human T cells. Differential response of T-cell subpopulations. J Clin Invest 1979; 64: 1188–1195.
47. Chouaib S, Chatenoud L, Klatzmann D, Fradelizi D. The mechanisms of inhibition of human IL 2 production. II. PGE_2 induction of suppressor T lymphocytes. J Immunol 1984; 132: 1851–1857.
48. Walker C, Kristensen F, Bettens F, DeWeck AL. Lymphokine regulation of activated (G_1) lymphocytes. I. Prostaglandin E_2-induced inhibition of interleukin 2 production. J Immunol 1983; 130: 1770–1773.
49. Rincón M, Tugores A, López-Rivas A, Silva A, Alonso M, de Landázuri MO, López-Botet M. Prostaglandin E_2 and the increase of intracellular cAMP inhibit the expression of interleukin 2 receptors in human T cells. Eur J Immunol 1988; 18: 1791–1796.
50. Cunha-Neto E, Rizzo LV. Prostaglandin E_2 inhibits proliferation but not interleukin 2 production by phorbol ester plus calcium ionophore-activated murine T cell clones. Braz J Med Biol Res 1989; 22: 365–377.
51. Phipps RP, Lee D, Schad V, Warner GL. E-series prostaglandins are potent growth inhibitors for some B lymphomas. Eur J Immunol 1989; 19: 995–1001.
52. Jelinek DF, Thompson PA, Lipsky PE. Regulation of human B cell activation by prostaglandin E_2. Suppression of the generation of immunoglobulin-secreting cells. J Clin Invest 1985; 75: 1339–1349.
53. Webb DR, Wieder KJ, Rogers TJ, Healy CT, Nowowiewjski-Wieder I. Chemical identification of a prostaglandin-induced T suppressor (PITS). Lymphokine Res 1985; 4: 139–149.
54. Aune TM. Role and function of antigen nonspecific suppressor factors. CRC Critical Reviews in Immunology 1987; 7: 93–130.
55. Almawi WY, Murphy MG, Ogbaghebriel A, Pope BL. Cyclic AMP as the second messenger for prostaglandin E in modulating suppressor cell-activation by natural suppressor/cytotoxic cells. Int J Immunopharmacol 1987; 9: 697–704.
56. Fischer A, Durandy A, Griscelli C. Prostaglandin E_2-mediated monocyte suppressive activity-role in immunoregulatory disorders. In: Seligmann M, Hitzig WH (eds). Primary Immunodeficiencies. INSERM Symposium No. 16, Amsterdam: Elsevier/North-Holland Biomedical Press, 1980; 363–372.
57. Sillevis Smitt JH, Box JD, Hulsebosch HJ, Krieg SR. In situ immunophenotyping of antigen presenting cells and T cell subsets in atopic dermatitis. Clin Exp Dermatol 1986; 11: 159–166.
58. Ruzicka T, Simmet T, Peskar BA, Ring J. Skin levels of arachidonic acid-derived inflammatory mediators and histamine in atopic dermatitis and psoriasis. J Invest Dermatol 1986; 86: 105–108.

59. Fogh K, Herlin T, Kragballe K. Eicosanoids in skin of patients with atopic dermatitis: prostaglandin E_2 and leukotriene B_4 are present in biologically active concentrations. J Allergy Clin Immunol 1989; 83: 450-455.
60. Chapkin RS, Ziboh VA. Inability of skin enzyme preparations to biosynthetize arachidonic acid from linoleic acid. Biochem Biophys Res Commun 1984; 124: 784–792.
61. Chapkin RS, Ziboh VA, Marcelo CL, Vorhees JJ. Metabolism of essential fatty acids by human epidermal enzyme preparations: evidence of chain elongation. J Lipid Res 1986; 27: 945–954.
62. Morse PF, Horrobin DF, Manku MS, Stewart JCM, Allen R, Littlewood S, Wright S, Burton J, Gould DJ, Holt PJ, Jansen CT, Mattila L, Meigel W, Dettke TH, Wexler D, Guenther L, Bordoni A, Patrizi A. Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and clinical response. Br J Dermatol 1989; 121: 75–90.
63. Wright S, Burton JL. Oral evening-primrose-seed oil improves atopic eczema. Lancet 1982; ii: 1120–1122.
64. Anstey A, Quigley M, Wilkinson JD. Topical evening primrose oil as treatment for atopic eczema. J Dermatol Treatment 1990; 1: 199–201.
65. Miller CC, Ziboh VA. Gammalinolenic acid-enriched diet alters cutaneous eicosanoids. Biochem Biophys Res Commun 1988; 154: 967–974.
66. Miller CC, McCreedy CA, Jones AD, Ziboh VA. Oxidative metabolism of dihomogammalinolenic acid by guinea pig epidermis: evidence of generation of anti-inflammatory products. Prostaglandins 1988; 35: 917–938.
67. Miller CC, Tang W, Ziboh VA, Fletcher MP. Dietary supplementation with ethyl ester concentrations of fish oil (n-3) and borage oil (n-6) polyunsaturated fatty acids induces epidermal generation of local putative anti-inflammatory metabolites. J Invest Dermatol 1991; 96: 98–103.
68. Ham EA, Soderman DD, Zanetti ME, Dougherty HW, McCauley E, Kuehl FA Jr. Inhibition by prostaglandins of leukotriene B_4 release from activated neutrophils. Proc Natl Acad Sci USA 1983; 80: 4349–4353.
69. Hansen HS. Dietary essential fatty acids and in vivo prostaglandin production in mammals. Wld Rev Nutr Diet 1983; 42: 102–134.
70. Willis AL. The eicosanoids: an introduction and an overview. In: Willis AL (ed.). CRC Handbook of eicosanoids: prostaglandins and related lipids, vol. 1, part A, CRC Press, Boca Raton, Florida 1987; pp. 3–46.
71. Bourne HR, Lichtenstein LM, Melmon KL. Pharmacologic control of allergic histamine release in vitro: evidence for an inhibitory role of 3′,5′-adenosine monophosphate in human leukocytes. J Immunol 1972; 108: 695–705.
72. Hawk JLM, Black AK, Jaenicke KF, Barr RM, Soter NA, Mallett AI, Gilchrest BA, Hensby CN, Parrish JA, Greeves MW. Increased concentrations of arachidonic acid, prostaglandins E_2, D_2, and 6-oxo-$F_{1\alpha}$, and histamine in human skin following UVA irradiation. J Invest Dermatol 1983; 80: 496–499.
73. Pentland AP, Mahoney MG. Keratinocyte prostaglandin synthesis is enhanced by IL-1. J Invest Dermatol 1990; 94: 43–46.
74. Gollhausen R, Kaidbay K, Schechter N. UV suppression of mast cell-mediated whealing in human skin. Photodermatol 1985; 2: 58–67.
75. Bach M-A, Fournier C, Bach JF. Regulation of theta antigen expression by agents altering cyclic AMP level and by thymic factor. Ann NY Acad Sci 1975; 249: 316–319.
76. Mertin, J. and Stackpoole, A. Anti-PGE antibodies inhibit in vivo development of cell-mediated immunity. Nature 1981; 294: 456–458.
77. Schneid MP, Goldstein G, Hammerling U, Boyse EA. Lymphocyte differentiation from precursor cells in vitro. Ann NY Acad Sci 1975; 249: 531–540.
78. Bach MA. Differences in cyclic AMP changes after stimulation by prostaglandins and isoproterenol in lymphocyte subpopulations. J Clin Invest 1975; 55: 1074–1081.
79. Homo-Delarche F, Duval D, Papiernik M. Prostaglandin production by phagocytic cells of the mouse thymic reticulum in culture and its modulation by indomethacin and corticosteroids. J Immunol 1985; 135: 506–512.
80. Homo F, Russo-Marie F, Papiernik M. Prostaglandin secretion by human thymic epithelium: in vitro effects of steroids. Prostaglandins 1981; 22: 377–385.
81. Rinaldi-Garaci C, Favalli C, Del Gobbo V, Garaci E. Is thymosin action mediated by prostaglandin release? Science 1983; 220: 1163–1164.
82. Garaci E, Rinaldi-Garaci C, Del Gobbo V, Favalli C, Santoro G, Jaffe, BM. A synthetic analog of prostaglandin E_2 is able to induce *in vivo* theta antigen on spleen cells of adult thymectomized mice. Cell Immunol 1981; 62: 8–14.
83. Singh U, Owen JJT. Studies on the effect of various agents on the maturation of thymus stem cells. Eur J Immunol 1975; 5: 286–288.
84. Melnik BC, Plewig G. Atopy: a prostaglandin E precursor- and receptor-dependent defect in T-cell maturation and function? Br J Dermatol 1990; 123: 126–128.
85. Shipman PM, Schmidt RR, Chepenik KP. Relation between arachidonic acid metabolism and development of thymocytes in fetal thymic organ cultures. J Immunol 1988; 140: 2714–2720.
86. Strannegård Ö, Strannegård I-L, Rystedt I. Viral infections in atopic dermatitis. Acta Derm Venereol (Stockh) 1985; Suppl 114: 121–124.
87. Pottathil R, Chandrabose KA, Cuatrecasas P, Lang DJ. Establishment of the interferon-mediated antiviral state: role of fatty acid cyclo-oxygenase. Proc Natl Acad Sci USA 1980; 7: 5437–5440.
88. Chandrabose KA, Cuetrecasas P, Pottathil R, Lang DJ. Interferon-resistant cell line lacks fatty acid cyclooxygenase activity. Science 1981; 212: 329–331.
89. Dunbar LM, Bailey JM. Enzyme deletions and essential fatty acid metabolism in cultured cells. J Biol Chem 1975; 250: 1152–1153.
90. Mallett RB, Myint S, Holden CA. Phosphoinositide specific phospholipase C activity in atopic dermatitis. Poster 100, 21st Meeting of the European Society for Dermatological Research, Copenhagen, 1991.
91. Thestrup-Pedersen K. Immunology of atopic dermatitis. Acta Derm Venereol (Stockh) 1989; 69, Suppl 151: 77–83.
92. Wertz PW, Swartzendruber DC, Abraham W, Madison KC, Downing DT. Essential fatty acids and epidermal integrity. Arch Dermatol 1987; 123: 1381–1384.
93. Brenner RR. Nutritional and hormonal factors influencing desaturation of essential fatty acids. In: Holden RT (ed.), Essential fatty acids and prostaglandins, Progress in Lipid Research, vol 20, Pergamon Press, New York 1981; pp 41–47.
94. Saarinen UM, Kajosaari M, Backman A, and Siimes MA. Prolonged breast-feeding as prophylaxis for atopic disease. Lancet 1979; ii: 163–166.
95. Casimir G, Vermeylen D, Duchateau J. Neonatal serum IgE concentration as a predictor of atopy: advantages of breast feeding. Rev Med Brux 1983; 4: 323–326.
96. Gibson RA, Knebone GM. Fatty acid composition of human colostrum and mature breast milk. Am J Clin Nutr 1981; 34: 252–257.
97. Juto P. Elevated serum immunoglobulin E in T cell-deficient infants fed cow's milk. J Allergy Clin Immunol 1980; 66: 402–407.
98. Tainio V-M. Lymphocyte subsets in infants: relationship to feeding, atopy, atopic heredity and infections. Int Archs Allergy appl Immun 1985; 78: 305–310.
99. Kang K, Strannegård Ö, Strannegård I-L., Cooper K, Hanifin JM. Suppressor cell phenotype deficiency and its restoration by thymopoietin pentapeptide in atopic dermatitis. Monogr Allergy 1983; 18: 181–185.

100. Leung DYM, Hirsch RL, Schneider L, Moody C, Takaoka R, Shihua HL, Meyerson LA, Mariam SG, Goldstein G, Hanifin JM. Thymopentin therapy reduces the clinical severity of atopic dermatitis. J Allergy Clin Immunol 190; 85: 927–933.
101. Marshall GD Jr, Thurman GB, Goldstein AL. Regulation of in vitro generation of cell-mediated cytotoxicity. In vitro induction of suppressor T lymphocytes by thymosin. J Reticuloendothelial Soc 1980; 28: 141–149.
102. Happle R, Schnyder UW. Evidence for the Carter effect in atopy. Int Arch Allergy Appl Immunol 1982; 68: 90–92.
103. Küster W, Petersen M, Christophers E, Goos M, Sterry W. A family study of atopic dermatitis. Clinical and genetic characteristics of 188 patients and 2,151 family members. Arch Dermatol Res 1990; 282: 98–102.
104. Kramer MS. Does breast feeding help protect against atopic disease? Biology, methodology, and a golden jubilee of controversy. J Pediatr 1988; 112: 181–190.
105. Melnik BC, Plewig G. Is the origin of atopy linked to deficient conversion of ω-6-fatty acids to prostaglandin E_1? J Am Acad Dermatol 1989; 21: 557–563.
106. Sanders TAB, Naismith DJ. A comparison on the influence of breast feeding and bottle-feeding on the fatty acid composition of the erythrocytes. Br J Nutr 1979; 41: P619–623.
107. Carlson SE, Rhodes PG, Ferguson MG. Docosahexaenoic acid status of preterm infants at birth and following feeding with human milk or formula. Am J Clin Nutr 1986; 44: 798–804.
108. Gibson RA, Rassias G. Infant nutrition and human milk. In: Horrobin DF (ed.), Omega-6 essential fatty acids: pathophysiology and roles in clinical medicine. Alan Liss, New York 1990: pp 283–293.