

Pathophysiology of itching in urticaria and atopic dermatitis

Wahlgren C.-F. Pathophysiology of itching in urticaria and atopic dermatitis
Allergy 1992; 47: 65–75.

C.-F. Wahlgren

Department of Dermatology, Karolinska Hospital, Stockholm, Sweden

Key words: antihistamines; cyclosporin A; cytokines; histamine; measurement; pruritus; Pain-Track[®]; Symtrack[®]

Carl-Fredrik Wahlgren, M.D., Ph.D.,
Department of Dermatology
Karolinska Hospital
S-104 01 Stockholm
Sweden

Accepted for publication 5 March 1992

Introduction

Itching, or pruritus, is defined as an unpleasant sensation which provokes the desire to scratch (1). From a phylogenetic point of view, itching can be regarded as a "physiological" and well-adapted nociceptive sensation that induces scratching in order to remove potentially noxious or damaging stimuli, such as ectoparasites, fibres or chemicals from the skin surface. When itching occurs as a symptom of skin disease or internal disorder, its nociceptive function is dubious, as scratching can lead to further damage of the skin, increasing the inflammation and pruritus, i.e. a vicious "itch-scratch" circle is initiated. Mild pruritus may occur in people's everyday life and therefore it is often overlooked as a trivial phenomenon, but intense itching can be extremely distressing and as disabling as severe pain.

Today's knowledge of the pathophysiology of itching is based on studies of human subjects, as no research models for the investigation of itching in animals are established (2). Although scratching often occurs in animals, there is no definite proof that it always reflects the sensation of itching (3). The highly subjective nature of pruritus makes it an intricate task for the investigator to evaluate. To circumvent the problem of measuring such a subjective symptom, some investigators have developed methods for measurement of scratching, as this is the objective correlate to itching. The methods have included various nocturnal movement-sensitive

meters secured to the patient's limbs, e.g. monitoring of forearm muscle potentials (4–6), the use of modified self-winding watches (7), electromagnetic movement detectors (8) or paper strain gauges (9). Other methods have employed bed vibration transducers attached to hospital bed-legs (7), or a movement-sensitive radar beside the patient's bed (10). The major gain with the nocturnal scratch recordings has been an increased knowledge of scratching behaviour during different stages of sleep (5). Due to the technical requirements, these investigations have been restricted to inpatients. Sometimes the results of the scratch recordings have been validated by correlating them with subjective ratings of itching (7,8), i.e. in the end one has to rely upon the patient's assessment of his own symptom, which has long been well accepted in pain research (11).

In clinical studies, various scales for rating itch intensity have been used, but their validation has received very little attention. However, some recent studies (12–15) have focused on the evaluation of rating scales used for assessing experimentally induced itching. Such studies, which have the advantage that the itch-provoking stimulus is controlled, have shown that it is possible to obtain a dose-response curve between the stimulus strength and the itch response, i.e. a weaker stimulus produces less itching than a stronger stimulus. This indicates that it is possible for a subject to assess the itch intensity accurately. The visual analogue scale (VAS) is a rating scale used for measuring various subjec-

tive feelings (16). This scale can be used also for assessing itch intensity, both in experimentally induced pruritus (14, 15) and in clinical disease (17). Furthermore, both conventional retrospective rating forms completed twice daily and a new computerized technique for continuous recording of pruritus are valid for measuring itch intensity in clinical disease (17). The latter method (Pain-Track®, Symtrack®) consists of portable microcomputers carried by the patients all day and night (17–20). Its main advantages are possibilities for frequent sampling, surveillance of compliance, analysis of a large amount of data, and the possibility to study changes in the itch intensity over the day (17).

The qualitative aspects of the itch sensation in various diseases have not been investigated systematically. There is no "itch questionnaire" analogous to the "McGill pain questionnaire" (21) which, in addition to an intensity rating scale, contains qualitative verbal terms to be chosen as a specification of the pain sensation.

Neurophysiology

Itching can be elicited by chemical, electrical, mechanical and thermal stimulation (22, 23). No morphological structure has been identified as specific receptor for the itch sensation, but it is assumed that "itch receptors" are linked to the free nerve endings of C-fibres close to the dermo-epidermal junction (22). The impulses set up in the thin, non-myelinated, slowly conducting C-fibres enter the spinal cord via the dorsal horn, then ascend in the contralateral spinothalamic tract, pass via thalamus and end in the somatosensory cortex of the post-central gyrus (24).

Itching and pain are related phenomena, and it was previously believed that itching was equal to subthreshold pain, i.e. with increased activity in the C-fibres the perceived sensation changed from itching to pain. Today, itching and pain are considered as 2 separate sensory modalities (23). The reasons for this are: a) that both sensations can be felt simultaneously, b) that if the epidermis is removed itching cannot be elicited, whereas pain can still be provoked, c) that itching and pain evoke different motor responses (scratching and withdrawal, respectively), d) that opioids provoke itching, but relieve pain, and, e) recent neurophysiological findings. By inserting microelectrodes percutaneously into peripheral C-fibres of conscious volunteers, Torebjörk & Ochoa (25) showed that electrical stimulation of some C-fibres provoked itching, whereas stimulation of other C-fibres induced pain. If itching was induced, increased stimulation frequency gave an increased itch intensity, but itching never changed to pain. Further studies, where pruritus was provoked

by electrical stimulation (12) or histamine iontophoresis (14), have confirmed this.

The central mechanisms involved in the modulation, interpretation and processing of pruritus are completely unknown, but undoubtedly the central nervous system has a great influence on the perception of itching. For example, emotional stress or anxiety can aggravate pruritus (26), whereas distraction can relieve it.

It is not fully understood why the natural consequence of itching, i.e. scratching or rubbing of the skin, relieves itching, but several mechanisms may be involved. The "gate-control" theory was introduced by Melzack & Wall (27) to explain why mechanical stimulation reduces pain. They suggested that activity in afferent large-diameter myelinated A-fibres, elicited by vibration or touch, inhibits the activity in afferent small-diameter C-fibres reaching the spinal cord, i.e. A-fibre input closes the "gate" for C-fibre input. It is not known whether this phenomenon is applicable to the itch sensation, but if so, it may explain why rather mild mechanical stimulation of the skin temporarily relieves mild pruritus. Furthermore, it is known that itching cannot be induced experimentally in an area previously exposed to pain ("antipruritic state") (28). Scratching of the skin is a fairly strong mechanical stimulus also activating nociceptors, and the nociceptive input appears to be particularly important for induction of the "antipruritic state" i.e. pain seems to inhibit itching.

If a mild mechanical stimulus is applied to the skin in an area surrounding that exposed to a pruritic stimulus, such as a mosquito bite or an intradermal injection of histamine, itching is often perceived instead of touch. This phenomenon of cutaneous hyperaesthesia is called "itchy skin" (28) or "alloknesis" (29). The underlying neurophysiological mechanisms are not known in detail, but the condition has several features in common with secondary hyperaesthesia, which appears to be due to an altered central processing of mechanoreceptive input (Torebjörk, personal communication). The state of "itchy skin" may be of considerable importance in pruritic skin diseases if trivial mechanical stimulation, such as light touch or friction, of "uninvolved skin" next to pruritic skin lesions is felt as itching. It is important to note that "itchy skin" is not equivalent to a lowered itch threshold. The latter indicates that pruritus is provoked by a less intense pruritogenic stimulus (e.g. a lower histamine concentration), but not that touch is perceived as itching, which is the case in the state of "itchy skin".

Mediators of itching

Most pruritic dermatoses (e.g. infestations, urticaria, eczema, lichen planus, dermatitis herpetiformis) are

associated with a cutaneous inflammation where various inflammatory mediators are produced. Pruritogenic mediators are assumed to act directly upon free nerve endings of the C fibres close to the dermo-epidermal junction, or to act indirectly by stimulating release or activation of substances that in turn stimulate these nerve endings. On the other hand, cutaneous inflammation is not always associated with pruritus (e.g. acne and discoid lupus erythematosus) and inflammation of the skin is not a prerequisite for itching, as it is not observed in pruritic internal diseases (e.g. uraemia and cholestasis). The pathomechanisms of most pruritic dermatoses and internal diseases are still unknown.

No single or principal pruritogenic mediator is identified, although histamine was for long considered the unique, direct, chemomediator of clinical pruritus. During the 1950's, it was shown that proteases could cause itching, and Arthur & Shelley (22, 30) suggested that proteolytic enzymes produced by cellular infiltrates in the skin, by blood in the skin capillaries, by damaged epidermal cells, or by microorganisms on the skin surface may contribute to clinical pruritus in various diseases. The discovery and identification in biochemical research of various new inflammatory mediators have allowed studies of their pruritogenic properties, as summarized in Table 1. Most proteases and peptides have

turned out to be histamine liberators, and the itching provoked by most of these substances can therefore be blocked by antihistamines (31). Kallikrein and papain, however, elicit a burning itch without the release of histamine from dermal mast cells (32, 33). Prostaglandins (34–37) and endorphins (38, 39) induce no or only weak itching on their own, but potentiate histamine-induced itching, i.e. they may act as peripheral modulators of itching.

The central mediators or transmitters of pruritus are unknown, but recent findings indicate a role for endorphins, i.e. endogenous peptides with morphine-like antinociceptive activity. These neurogenic peptides are found in both peripheral and central nerve fibres and they are assumed to be involved in the endogenous control of pain (40). If morphine is injected into the cisterna cerebellomedullaris in certain animals, a violent scratching syndrome is provoked (41). In man, itching is a well-known side-effect in patients receiving epidural or spinal opiates and such induced itching is reversed by administration of the opiate antagonist naloxone (42). In a double-blind, randomized, placebo-controlled study of patients with chronic urticaria or atopic dermatitis (AD), a single oral dose of nalmefene, a potent opiate antagonist, significantly reduced itching, but adverse effects were frequent (43). The itch-relieving effect of opiate antagonists suggests a role for endorphins

Table 1. Pruritogenic properties of some inflammatory mediators, investigated by intradermal injections in human skin

Group	Substance	Pruritus	Comment	Reference
Amines	Histamine	+	Classical chemomediator of itching	(44, 45)
	Serotonin	(+)	Not present in human mast cells, but released when platelets aggregate; itching potentiated by prostaglandins	(121)
Proteases	Trypsin	+	Histamine liberator	(22, 122)
	Chymase	+	Histamine liberator	(122)
	Papain	+	Burning itch without visible skin changes; no histamine releasing effect; itching potentiated by prostaglandins	(30, 33, 35)
	Kallikrein	+	Burning itch without visible skin changes; no histamine releasing effect	(32)
Peptides	Bradykinin	(+)	Histamine liberator	(32)
	Secretin	+	Histamine liberator	(123)
	Substance P	+	Histamine liberator	(123, 124)
	Neurotensin	+	Histamine liberator	(123)
	VIP	+	Histamine liberator	(123)
	Endorphins	0/(+)	Potentiates histamine-induced itching without histamine release or formation of prostaglandins	(38)
Eicosanoids	Prostaglandins	0/(+)	Potentiates itching induced by histamine, serotonin and papain	(34–37, 121)
	Leukotrienes	0		(125)
	HETE	0	Unpublished data	Hägermark, personal communication
Phospholipids	PAF	+	Histamine liberator	(126)

0=no itching; (+)=weak itching; +=itching; VIP=vasoactive intestinal polypeptide; HETE=hydroxyeicosatetraenoic acid; PAF= platelet activating factor.

and opiate receptors in the central transmission of pruritus.

Urticaria

Urticaria is a condition characterized by transient wheals in the skin resulting from acute dermal oedema. The pathogenesis involves immunological, non-immunological and idiopathic mechanisms. In the 1920's, Lewis showed that intradermal injection of histamine causes itching and a vascular "triple response" in the skin comprising a local redness, wheal and axon-reflex-mediated flare reaction (44, 45), i.e. the same symptoms as in urticaria. Histamine, since then the classical chemomediator of itching, is released from activated skin mast cells and is the main pruritogenic mediator in most cases of urticaria. In fact, urticaria is the only disease where the main itch-provoking substance is known. In all other pruritic diseases the pruritogens are unknown. Other vasoactive mediators of varying cellular origin may, however, also be involved in the pathogenesis of urticaria, e.g. prostaglandins and neuropeptides (46–48), and these substances may therefore contribute to the itching in the whealing disorders.

Histamine-induced itching is mediated through H_1 receptors in human skin, whereas the contribution from H_2 receptors seems doubtful (49, 50). The pruritus is associated with a visible "triple response" and the histamine dose required to induce itching is higher than that needed to provoke the vascular responses (30). Accordingly, histamine-induced itching without a visible wheal and flare reaction is unlikely. The individual lesions in urticaria are often most pruritic at onset. Repeated intradermal injections of histamine lead to tachyphylaxis in the skin, i.e. further injections of histamine lead to gradually decreased itching and vascular responses (44, 51, 52). This phenomenon, together with local depletion of histamine stores in skin mast cells, is assumed to explain the short duration (a few hours) of the individual lesions in urticaria, whereas new lesions continue to develop at new sites.

The itch-relieving effect of H_1 -receptor antagonists in most cases of urticaria is well documented (46, 50), although some patients respond poorly, indicating that other pruritogenic inflammatory mediators may be involved, as well.

Atopic dermatitis

General aspects

AD is a genetically based (53), pruritic, chronically relapsing inflammatory skin disease, with typical clinical morphology and distribution, frequently as-

sociated with a personal history of respiratory atopy or a family history of respiratory atopy and/or AD (54). In addition to these major criteria, several minor features can be listed (54), e.g. early age at onset, dryness of the skin, tendency toward cutaneous infections, recurrent conjunctivitis, increased serum IgE level, positive immediate skin test reactions and various functional, vascular abnormalities. The aetiology of AD is unknown, but it is assumed to be multifactorial (55, 56). The primary pathogenic mechanisms are unknown, although research during recent decades has shown several pharmacophysiological, biochemical and immunological abnormalities, as extensively reviewed by several authors (55, 61). The role of IgE in AD is unclear, and hence, the term "atopic" is sometimes criticized. The frequency of elevated serum IgE levels seems to vary with the severity of AD and the presence of a concomitant respiratory atopy (55). The IgE bound to mast cells and basophilic granulocytes is involved in the pathogenesis of the immediate hypersensitivity reaction, including the late-phase reaction, but it is not proven that these reactions are involved in the pathogenesis of AD, although it has been suggested (62). Another possible role for IgE in AD is suggested by the finding of IgE bound via low-affinity Fc-IgE receptors ($Fc\epsilon R2/CD23$) on Langerhans' cells in involved skin, and to a lesser extent in uninvolved skin, of AD patients with elevated serum IgE levels (63–66). Epidermal Langerhans' cells may bind and present allergens to T lymphocytes, inducing an allergen-specific inflammatory response (63, 67). The significance of the immune system and lymphocytes in AD is supported by the fact that atopy has been transferred with bone marrow transplantation from an atopic donor to a non-atopic receiver (68), and conversely, that transplantation of a normal bone marrow to patients with the Wiskott-Aldrich syndrome has cured their eczematous lesions (69, 70) which are indistinguishable from AD.

Histochemical and immunohistochemical findings

The microscopic features of AD vary with the nature of the clinical lesion. The acute lesion is characterized by epidermal intercellular oedema, and epidermal and perivascular dermal inflammatory infiltrates. The chronic lichenified lesion shows acanthosis and hyperkeratosis, and dermal inflammatory infiltrates in both perivascular and intervascular locations. The inflammatory cellular infiltrates consist predominantly of lymphocytes and macrophages. The T-helper/T-suppressor cell ratio in the skin is approximately 7:1 (71). The number of mast cells is increased in lichenified plaques, but not in acute lesions or in normal-appearing skin (72, 73). Only occasional neutrophils, eosinophils and basophils

are noted (72). Although accumulation of eosinophils in the skin is not a prominent feature in AD, the finding of deposits of major basic protein in AD lesions indicates that these cells degranulate in the skin in such patients (74). Venular changes are observed in both lesional and normal-looking AD skin comprising endothelial cell hypertrophy and homogeneous thickening of the basement membrane (72).

Clinical itching and scratching

Pruritus is a hallmark of AD, and the patients judge the severity of their eczema more by the itch intensity than by the appearance of the skin lesions. Itching is often more intense in the evening and at night, although peaks occur also in the morning (17). Itching can be aggravated by various factors, each having different importance in the individual patient. In a study of 85 adult AD patients, detailed interviews revealed that itching was provoked by heat/perspiration in 96% of the patients, by wool fibres in 91%, by emotional stress in 81%, by certain foods in 49%, by alcohol in 44% and by common colds in 36% (20).

Many of the lesions in AD patients are secondary to scratching of the skin, which leads to lichenification and excoriations, increasing the cutaneous inflammation and in turn provoking more itching, i.e. a vicious circle of itching and scratching is initiated. The use of mechanical scratching devices is frequent and was admitted by 38% of the AD patients in one study (20). Many patients tend to scratch at moments of emotional tension or frustration. The psychological component of the scratching behaviour is complex, but it has been stated that it sometimes includes a component of pleasure or somatization of emotions. Furthermore, scratching can be a conditioned response, and an experimental study shows that patients with AD are more prone to develop a conditioned scratching response than controls (75).

Studies of AD patients employing nocturnal limb-movement sensitive meters show that 2–38% of the night time is associated with scratching (4, 9). Sleepers scratch predominantly with the hands, but increased leg movements also occur, reflecting a nocturnal restlessness (7, 8). In fact, a considerable amount of energy can be consumed in nocturnal scratching and restlessness (7). Scratching is more frequent in superficial stages of orthodox sleep than in deeper stages, whereas the paradoxical sleep (rapid eye movement) is in between (5). The duration of the scratching bouts is fairly constant for each individual and not related to the depth of sleep (5). Some sedative drugs, such as trimeprazine and trimipramine, modestly reduce nocturnal scratching,

probably because they reduce the time spent in the superficial stage of orthodox sleep when scratching is most frequent (6).

Pathophysiology of itching

The mechanisms causing pruritus in AD are unknown. Rajka (55) has suggested that 2 components can be recognized: first, itching induced by various immunological or non-immunological stimuli, and secondly, an increased itch sensitivity in the skin, observed as reduced itch thresholds or prolonged itch durations for pruritic stimuli.

The increased itch sensitivity can be illustrated by using wool fibres of medium to coarse thickness, which provoke a stronger itch response in patients with AD than in healthy controls (76), but the increased itch sensitivity does not seem valid for all pruritogenic substances. When various doses of histamine are injected intradermally in AD patients and healthy controls, the dose-response curves for the itch responses do not differ significantly between the 2 groups, indicating that they are equally able to discriminate between weak and strong histamine concentrations, and that AD patients are neither significantly more sensitive nor refractory to histamine (76). Wool fibres also provoke a qualitatively different response, as significantly more AD patients than controls feel a "pure itching" without any pricking sensation (76). This may reflect the state of "itchy skin", where mild mechanical stimulation is perceived as itching and not as touch, and this phenomenon may be added as a third component of importance for the itching in patients with AD.

However, the pruritic mediator(s) of AD must be considered as the most important component. This substance or substances, as well as its/their cellular origin, remains to be identified.

Histamine

Much interest has focused on mast cells and basophils, as they produce histamine as well as other inflammatory mediators. The number of mast cells in lichenified AD plaques is increased, but the peripheral basophilic granulocytes are normal in number. On the other hand, *in vitro* studies of basophils show an abnormal function with increased (77) or faster histamine releasability (78). Histamine is the most thoroughly studied pruritogen and has been a persevering candidate as chemomediator of pruritus in AD. During the 1930's, it was suggested that histamine might be involved in the pathogenesis of AD, as studies showed that intramuscular injections of histamine increased the skin temperature in the flexures in AD patients but not in controls (79). Stud-

ies during the 1960's showed increased histamine levels in involved and uninvolved AD skin (80, 81), although this was not specific for AD (81). Recent studies employing a more sensitive laboratory technique have failed to confirm significantly elevated skin histamine levels (82). Plasma histamine levels are normal (82) or sometimes raised (83) in patients with AD.

However, there are several arguments against histamine being the main pruritogen in patients with AD. When histamine is injected intradermally, itching is nearly always accompanied by a visible vascular response (20) and the dose required to elicit pruritus is higher than that needed to provoke whealing (30). The itching in patients with AD is not associated with whealing. Furthermore, the long-lasting itching of the individual lesions in AD patients is not compatible with repeated or continuous histamine stimulation, which would induce tachyphylaxis to histamine in the skin (44, 51, 52). Finally, the antipruritic effect of H_1 -receptor antagonists in placebo-controlled studies of AD patients is not convincing, whereas their antipruritic effect in most cases of urticaria is generally prompt.

The study of pruritus and the antipruritic effect of drugs is a challenge for the clinical investigator. Several studies have been published concerning the antipruritic effect of antihistamines in both children and adults with AD, but most of them can be criticized as they do not meet essential design criteria for the clinical evaluation of antipruritic drugs. A double-blind, randomized study design is required and placebo must be included (84, 85), as the subjective symptom of itching is highly influenced by any medication, whether active or not (86, 87). By definition the patient himself has to assess the magnitude of itching, not the investigator of the study or the parents of a pruritic child, and the itch recording method has to be described carefully. A cross-over design has the advantage that the patient is his/her own control, minimizing the influence of individual factors, such as severity of eczema, flare factors and subjective reading of the rating scales.

If these basic requirements are applied, few studies of the itch-relieving effect of antihistamines in AD patients remain to review. In a double-blind, randomized, cross-over trial, where itching was rated in 16 AD patients using daily VAS forms, chlorpheniramine alone or chlorpheniramine plus cimetidine, given for 4 weeks each, did not relieve pruritus better than placebo (88). Three days' treatment with a new non-sedative H_1 -receptor antagonist, LN2974, failed to reduce itching recorded with VAS forms and nocturnal scratching recorded with limb-movement meters in a double-blind, randomized, placebo-controlled, cross-over study of 10 adults with AD (89). On the other hand, a double-blind, random-

ized, placebo-controlled, but parallel study with completing AD patients showed that 10 days' therapy with either of the 2 non-sedative antihistamines, terfenadine (180 mg/day) or acrivastine (24 mg/day), significantly relieved itching, rated with VAS forms, compared with placebo (90). Two subsequent double-blind, randomized, placebo-controlled, cross-over studies have failed to confirm these results. In one study completed with 24 AD patients, who rated itching twice daily on VAS forms, 7 days' treatment with terfenadine (240 mg/day) did not relieve itching more than placebo (91). In another trial involving 25 patients with AD, the antipruritic effect of the non-sedative antihistamine clemastine (4 mg/day) and the non-sedative antihistamine terfenadine (120 mg/day) was compared with that of placebo (18). The itch intensity was recorded continuously using a computerized method for self-assessment (Pain Track[®]). The treatments were given for 3 days each and the computerized itch recordings from days 1 and 3 were analysed. Intradermal histamine injections showed that both antihistamines had a significant H_1 -receptor blocking effect in the skin, confirming that the patients had taken the drugs as requested and that significant concentrations were achieved in the skin. In spite of this, and the fact that clemastine induced a significant sedation, neither clemastine nor terfenadine relieved the patients' clinical itching better than placebo. These findings (18), in combination with the previously mentioned placebo-controlled cross-over studies (88, 89, 91), support the view that histamine is not of major importance in the pathogenesis of pruritus in AD. Furthermore, sedation with antihistamines is not necessarily associated with itch relief (18, 20), which has previously been suggested by results from open studies of itching and scratching (92).

The results of experimental studies suggest that some antihistamines, in addition to their H_1 -receptor antagonizing effect, may have other effects, such as inhibiting the release of histamine (93, 94) and leukotrienes from mast cells (94), or inhibiting chemotaxis of eosinophils (95). The possible relevance of these experimental findings to the relief of clinical itching in AD patients is still completely unknown.

Eosinophil-derived toxic proteins

Blood eosinophilia is common in patients with AD. Disease severity and personal or family history of respiratory atopy are important factors in determining high blood eosinophil levels in these patients (96). The eosinophilic granulocytes contain, in their granules, various toxic proteins: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) and eosinophil peroxidase. Increased serum levels of MBP (97) and

ECP (98), and deposits of MBP in lesional skin (74) occur in patients with AD. Moreover, cutaneous eosinophils are present in positive patch tests with specific aero-allergens in AD patients (99). The role of the eosinophils in AD is, however, unknown. MBP *in vitro* induces histamine release from rat mast cells and human basophils (100), and intradermal injections of MBP, ECP or EDN into human skin induce a wheal and flare reaction (101). As whealing is not observed in AD lesions, it is unlikely that such a mechanism is important in the pathogenesis of itching in AD patients.

Cytokines

AD, allergic contact dermatitis, and lichen planus are examples of diseases where itching is a prominent feature. They have in common an inflammatory mononuclear cellular infiltrate consisting predominantly of lymphocytes and macrophages in the papillary dermis close to the dermo-epidermal junction, where the free nerve endings of the C-fibres are located. On activation, these mononuclear cells produce various cytokines, i.e. soluble mediators with many inflammatory and immunoregulatory effects, interacting in a complex network. Experimental data from peripheral blood T cells suggest that an imbalance in the interleukin-4/interferon- γ ratio may be of great importance in the mechanisms involved in AD (59). Techniques for culturing skin-infiltrating lymphocytes obtained via skin biopsies from lesional AD skin have recently been introduced (102–105) and offer an exciting possibility of studying the functional activity and spectrum of cytokine production of lesional skin lymphocytes. Such *in vitro*-expanded cultures of AD-skin-derived lymphocytes, stimulated with mitogens or allergens, produce interleukin-4, granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumour necrosis factor- α , whereas the production of interferon- γ is reduced or absent (103–105).

The question arises whether cytokines are pruritogenic. This has not been investigated methodically, but, interestingly, pruritus has been reported as a side effect in patients treated with certain cytokines. Injections of recombinant human GM-CSF can provoke local erythema and pruritus at the injection site (106). When recombinant human interleukin-2 (rhIL-2) is given intradermally to patients with lepromatous leprosy to reconstitute cell-mediated immunity in their cutaneous lesions, an induration appears at the injection site (107), accompanied by local itching (Kiessling, personal communication). Furthermore, intravenous infusion of rhIL-2 to cancer patients frequently provokes a widespread erythema and itching of the skin, and a peripheral blood eosinophilia (108). Immunohistochemical investigation

of skin biopsy specimens from these patients has shown the presence of activated T lymphocytes in the papillary dermis (108). As erythema and itching are not relieved by antihistamines or indomethacin, histamine or prostaglandins are unlikely to be the major cause of these skin symptoms (108). These findings, in fact, resemble some of those encountered in patients with AD.

In recent years, cyclosporin A (CSA), a cyclic polypeptide with potent immunosuppressive effects, has been used for the treatment of various inflammatory dermatoses and in several case reports the itch-relieving effect of oral CSA in various diseases, such as AD, lichen planus, Sézary syndrome and mycosis fungoides, is pointed out. Therefore, we initiated a double-blind, randomized, placebo-controlled study of the antipruritic effect of 10 days' treatment with oral CSA (5 mg/kg/day) in 10 adults with AD (19, 20, 109). Evaluation was based on computerized itch recording (Symtrack[®]), clinical scoring and examination of skin biopsy specimens. CSA significantly reduced the itch intensity, the eczema score and the number of peripheral blood eosinophils. An analysis of the percentage of time awake without pruritus on days 9–10 of CSA therapy revealed that 4/10 AD patients were completely free from itching, 2/10 spent more than 90% of the day without itching, whereas 4/10 were never free from itching. On days 9–10 of the placebo period, 9/10 patients spent no time without pruritus. The onset of the antipruritic effect differed, but 6/10 had an effect within days 2–4. In 1/10, no itch-relieving effect occurred within the 10 days of active therapy, although the eczema score clearly decreased. However, relapses were seen within 2–30 days of completion of CSA therapy. In at least half of the patients, CSA reduced the number of CD3+, CD4+, HLA-DR+, IgE+, CD23+ (low-affinity Fc-IgE receptor+), intercellular adhesion molecule-1+ (ICAM-1+) and EG2+ ("activated" eosinophils) cells in lesional skin. The presence or absence of, or changes in, any of these markers, did not strictly parallel the clinical itch intensities in the patients. It cannot be concluded that the immunohistochemical alterations observed during active therapy are specific for CSA. It is possible that they, in fact, may occur in any successful treatment of AD patients. CSA therapy does not decrease the serum IgE level in patients with AD (110). Furthermore, open studies show that immediate responses to intradermally injected histamine (111), and immediate- and late-phase reactions to intradermally injected allergen (110) are significantly increased during treatment with CSA. As the patient's eczema was markedly improved (110), the importance of the immediate/late-phase type-I hypersensitivity reactions in the pathogenesis of AD seems doubtful.

The mechanism of action of CSA in AD is not yet understood. A major effect of CSA is the inhibition of production of T cell-derived cytokines (112) but, in addition, CSA also affects a variety of other cells. For example, CSA *in vitro* has an antiproliferative effect on keratinocytes and endothelial cells (113), and inhibits the release of histamine from human lung mast cells (114), although the concentrations required seem to be higher than those needed to inhibit IL-2 production from T lymphocytes. Since cytokine therapy can provoke itching as a side effect and since CSA inhibits the production of various cytokines, it is possible that such mediators, directly or indirectly, alone or in concert, may be of importance in the pathogenesis of itching in AD.

Neuropeptides

Cutaneous nerves in lichenified plaques of AD patients reveal demyelination and fibrosis (72), but these morphological changes may be secondary to the repetitive trauma of scratching (72), as degenerative changes in nerve fibres occur also in other pruritic dermatoses where scratching is prominent (115). Sensory nerve fibres are found in the dermis and basal epidermis as free or specialized nerve endings. Examination of neuronal structures in the skin employing various immunohistochemical markers (e.g. protein S-100, protein gene product 9.5) has not shown any differences between lesional/non-lesional AD skin and skin from normal controls (Johansson & Wahlgren, unpublished data). However, the distribution and localization of some neuropeptides in lichenified AD plaques differ from those seen in normal subjects. Substance P-positive nerve fibres perivascularly in papillary dermis and neuropeptide Y-positive epidermal dendritic cells are frequently observed in AD patients, but not in healthy subjects, whereas the staining patterns for calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) do not differ between the groups (116). The importance of these findings is not clear, but it has been suggested that neuropeptides may form a link between the nervous system and cutaneous inflammation. Such a model may explain, for example, the well-known association between emotional stress, erythema and itching. Another possible explanation of why itching often develops in association with erythema or sweating, may be the fact that C-fibres are readily activated (lowered itch threshold) if the skin temperature is raised (51). Nevertheless, the primary factor that activates the C-fibres in these situations is unknown. When neuropeptides, such as substance P or neurotensin are injected intradermally, they induce itch responses that do not differ between AD patients and healthy controls (117). Most neuropeptides, however, are

histamine liberators where pruritus can be blocked by antihistamine (see Table 1), disfavours their role as primary pruritogens in AD.

Dry skin

Dry skin ("xeroderma", "asteatosis") is a frequent finding in patients with AD. It is defined as a roughened skin texture with fine scaling but without erythema. The underlying pathomechanisms are probably heterogeneous, but dry skin may be the sequelae of an otherwise invisible inflammation (118), or involve abnormalities in epidermal lipid metabolism (119). It is generally accepted that dry skin is inclined to itch, but the mechanism of itching in dry skin is not established. The water-binding capacity is decreased and the transepidermal water loss is raised in dry skin of AD patients (120), reflecting a defect skin barrier (120). This allows the penetration of irritants into the skin and this may cause itching. Alternatively, assuming that dry skin is associated with a mild cutaneous inflammation, pruritus may be provoked by pruritogenic inflammatory mediators. Some skin manifestation in AD, such as dry skin, erythema, itching and increased transepidermal water loss, show similarities with those of essential fatty-acid-deficient animals. Abnormalities of essential fatty-acid metabolism may play a role in the pathogenesis of AD and placebo-controlled clinical trials show a therapeutic and antipruritic effect of gamma linolenic acid (60), although the mechanisms for the antipruritic action are unknown.

Conclusions

Histamine, the classical chemomediator of itching, is the major pruritogen in most cases of urticaria and here the pruritus is relieved by H₁-receptor antagonist whether sedative or not. In AD, the pathomechanism of itching is unknown, but it is suggested that the primary factor is pruritus provoked by one or more inflammatory mediators. Such a mediator or mediators, and their cellular origin, remain to be defined. Most evidence supports the view that histamine is not the major pruritogen in AD, and this disqualifies several other pruritogenic inflammatory mediators, as many of these are histamine liberators. Therefore, the use of H₁-receptor antagonists as antipruritic drugs in patients with AD appears to be inappropriate. Other factors of importance in the pathogenesis of itching in AD are the increased itch sensitivity (lowered itch threshold and increased itch response) to some, but not all pruritogens, and probably the phenomenon of "itchy skin", where mild mechanical stimulation of the skin is perceived as itching.

References

1. HAFENREFFER S. Nosodochium, in quo cutis, eique adherentium partium, affectus omnes, singulari methodo, et cognoscendi et curandi fidelissime traduntur. Ulm: Kühn, B, 1660: 98–102.
2. WOODWARD DF, CONWAY JL, WHEELER LA. Cutaneous itching models. In: MAIBACH HI, LOWE NJ, eds. Models in dermatology, vol 1. Basel: Karger, 1985: 187–95.
3. DE CASTRO-COSTA M, GYBELS J, KUPERS R, VAN HEES J. Scratching behaviour in arthritic rats: a sign of chronic pain or itch? *Pain* 1987; 29: 123–31.
4. SAVIN JA, PATERSON WD, OSWALD I. Scratching during sleep. *Lancet* 1973; 2: 296–7.
5. SAVIN JA, PATERSON WD, OSWALD I, ADAM K. Further studies of scratching during sleep. *Br J Dermatol* 1975; 93: 297–302.
6. SAVIN JA, PATERSON WD, ADAM K, OSWALD I. Effects of trimeprazine and trimipramine on nocturnal scratching in patients with atopic eczema. *Arch Dermatol* 1979; 115: 313–15.
7. FELIX R, SHUSTER S. A new method for the measurement of itch and the response to treatment. *Br J Dermatol* 1975; 93: 303–12.
8. SUMMERFIELD JA, WELCH ME. The measurement of itch with sensitive limb movement meters. *Br J Dermatol* 1980; 102: 275–81.
9. AOKI T, KUSHIMOTO H, KOBAYASHI E, OGUSHI Y. Computer analysis of nocturnal scratch in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; Suppl 92: 33–7.
10. MUSTAKALLIO KK, RÄSÄNEN T. Scratch radar [abstract]. *Skin Pharmacol* 1989; 2: 233.
11. CHAPMAN CR, CASEY KL, DUBNER R, FOLEY KM, GRACEY RH, READING AE. Pain measurement: an overview. *Pain* 1985; 22: 1–31.
12. TUCKETT RP. Itch evoked by electrical stimulation of the skin. *J Invest Dermatol* 1982; 79: 368–73.
13. SIMONE DA, NGEOW JYF, WHITEHOUSE J, BECERRA-CABAL L, PUTTERMAN GJ, LAMOTTE RH. The magnitude and duration of itch produced by intracutaneous injections of histamine. *Somatosens Res* 1987; 5: 81–92.
14. HANDWERKER HO, MARGERL W, KLEMM F, LANG E, WESTERMAN RA. Quantitative evaluation of itch sensation. In: SCHMIDT RF, SCHAIBLE HG, VAHLE-HINZ C, eds. Fine afferent nerve fibers and pain. Weinheim: VCH, 1987: 461–73.
15. WAHLGREN CF, EKBLOM A, HÄGERMARK Ö. Some aspects of the experimental induction and measurement of itch. *Acta Derm Venereol (Stockh)* 1989; 69: 185–9.
16. AITKEN RCB. Measurement of feelings using visual analogue scales. *Proc R Soc Med* 1969; 62: 989–93.
17. WAHLGREN CF, HÄGERMARK Ö, BERGSTRÖM R, HEDIN B. Evaluation of a new method of assessing pruritus and antipruritic drugs. *Skin Pharmacol* 1988; 1: 3–13.
18. WAHLGREN CF, HÄGERMARK Ö, BERGSTRÖM R. The antipruritic effect of a sedative and an non-sedative antihistamine in atopic dermatitis. *Br J Dermatol* 1990; 122: 545–51.
19. WAHLGREN CF, SCHEYNUS A, HÄGERMARK Ö. Antipruritic effect of oral cyclosporin A in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1990; 70: 323–29.
20. WAHLGREN CF. Itch and atopic dermatitis: clinical and experimental studies. *Acta Derm Venereol (Stockh)* 1991; Suppl 165: 1–53.
21. MELZACK R. The McGill pain questionnaire: major properties and scoring methods. *Pain* 1975; 1: 277–99.
22. SHELLEY WB, ARTHUR RP. The neurohistology and neurophysiology of the itch sensation in man. *Arch Dermatol* 1957; 76: 296–323.
23. KEELE CA, ARMSTRONG D. Substances producing pain and itch. London: E ARNOLD, 1964.
24. SHAPIRO PE, BRAUN CW. Unilateral pruritus after a stroke. *Arch Dermatol* 1987; 123: 1527–30.
25. TOREBJÖRK HE, OCHOA JL. Pain and itch from C fiber stimulation [abstract]. *Soc Neurosci Abstr* 1981; 7: 228.
26. CORMIA FE. Experimental histamine pruritus I. Influence of physical and psychological factors on threshold reactivity. *J Invest Dermatol* 1952; 19: 21–34.
27. MELZACK R, WALL PD. Pain mechanisms: a new theory. *Science* 1965; 150: 971–9.
28. BICKFORD RG. Experiments relating to the itch sensation, its peripheral mechanism, and central pathways. *Clin Sci* 1937–1938; 3: 377–86.
29. LAMOTTE RH, SIMONE DA, BAUMANN TK, SHAIN CN, ALREJA M. Hypothesis for novel classes of chemoreceptors mediating chemogenic pain and itch. In: DUBNER R, GEBHART GF, BOND MR, eds. Proceedings of the Vth world congress on pain. Amsterdam: Elsevier Science Publishers BV, 1988: 529–35.
30. ARTHUR RP, SHELLEY WB. The role of proteolytic enzymes in the production of pruritus in man. *J Invest Dermatol* 1955; 25: 341–6.
31. HÄGERMARK Ö. Recent advances in the pathophysiology of itch. *Allergologie* 1989; 12: S139–42.
32. HÄGERMARK Ö. Studies on experimental itch induced by kallikrein and bradykinin. *Acta Derm Venereol (Stockh)* 1974; 54: 397–400.
33. HÄGERMARK Ö. Influence of antihistamines, sedatives, and aspirin on experimental itch. *Acta Derm Venereol (Stockh)* 1973; 53: 363–8.
34. GREAVES MW, McDONALD-GIBSON W. Itch: role of prostaglandins. *BMJ* 1973; 3: 608–9.
35. LOVELL CR, BURTON PA, DUNCAN EHL, BURTON JL. Prostaglandins and pruritus. *Br J Dermatol* 1976; 94: 273–5.
36. HÄGERMARK Ö, STRANDBERG K, HAMBERG M. Potentiation of itch and flare responses in human skin by prostaglandins E2 and H2 and a prostaglandin endoperoxide analog. *J Invest Dermatol* 1977; 69: 527–30.
37. HÄGERMARK Ö, STRANDBERG K. Pruritogenic activity of prostaglandin E2. *Acta Derm Venereol (Stockh)* 1977; 57: 37–43.
38. FJELLNER B, HÄGERMARK Ö. Potentiation of histamine-induced itch and flare responses in human skin by the enkephalin analogue FK 33-824, β -endorphin and morphine. *Arch Dermatol Res* 1982; 274: 29–37.
39. HÄGERMARK Ö. Itch and endorphins. In: RING J, BURG G, eds. New trends in allergy II. Berlin-Heidelberg: Springer-Verlag, 1986: 128–34.
40. BASBAUM AI, FIELDS HL. Endogenous pain control mechanisms: review and hypothesis. *Ann Neurol* 1978; 4: 451–62.
41. KOENIGSTEIN H. Experimental study of itch stimuli in animals. *Arch Dermatol Syphilol* 1948; 57: 828–49.
42. BALLANTYNE JC, LOACH AB, CARR DB. Itching after epidural and spinal opiates. *Pain* 1988; 33: 149–60.
43. MONROE EW. Efficacy and safety of nalmefene in patients with severe pruritus caused by chronic urticaria and atopic dermatitis. *J Am Acad Dermatol* 1989; 21: 135–6.
44. LEWIS T. The blood vessels of the human skin and their responses. London: Shaw & Sons, 1927.
45. LEWIS T, GRANT RT, MARVIN HM. Vascular reactions of the skin to injury. *Heart* 1927–1929; 14: 139–60.
46. CZARNETZKI BM. Urticaria. Berlin-Heidelberg: Springer-Verlag, 1986.
47. KOBZA BLACK A, GREAVES MW, CHAMPION RH, PYE RJ. The urticarias 1990. *Br J Dermatol* 1991; 124: 100–8.
48. SOTER NA. Acute and chronic urticaria and angioedema. *J Am Acad Dermatol* 1991; 25: 146–54.

49. HÄGERMARK Ö, STRANDBERG K, GRÖNNEBERG R. Effects of histamine receptor antagonist on histamine-induced responses in human skin. *Acta Derm Venereol* (Stockh) 1979; 59: 297-300.
50. OWEN DAA, H1- and H2-receptor antagonists. In: GREAVES MW, SHUSTER S, eds. *Pharmacology of the skin II*. Berlin-Heidelberg: Springer-Verlag, 1989: 227-37.
51. CORMIA FE, KUYKENDALL V. Experimental histamine pruritus II. Nature: physical and environmental factors influencing development and severity. *J Invest Dermatol* 1953; 20: 429-46.
52. STAHL-BÄCKDAHL M, HÄGERMARK Ö, LINS LE. The sensitivity of uremic and normal human skin to histamine. *Acta Derm Venereol* (Stockh) 1988; 68: 230-5.
53. SCHULTZ LARSEN F. Genetic aspects of atopic eczema. In: RUZICKA T, RING J, PRZYBILLA B, eds. *Handbook of atopic eczema*. Berlin-Heidelberg: Springer-Verlag, 1991: 15-26.
54. HANIFIN JM, RAJKA G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* (Stockh) 1980; Suppl 92: 44-7.
55. RAJKA G. Essential aspects of atopic dermatitis. Berlin-Heidelberg: Springer-Verlag, 1989.
56. RING J, RUZICKA T, PRZYBILLA B. The pathophysiology of atopic eczema: synopsis. In: RUZICKA T, RING J, PRZYBILLA B, eds. *Handbook of atopic eczema*. Berlin-Heidelberg: Springer-Verlag, 1991: 330-5.
57. HANIFIN JM. Pharmacophysiology of atopic dermatitis. *Clin Rev Allergy* 1986; 4: 43-65.
58. LEUNG DYM, GEHA RS. Immunoregulatory abnormalities in atopic dermatitis. *Clin Rev Allergy* 1986; 4: 67-86.
59. HANIFIN JM. Immunologic aspects of atopic dermatitis. *Dermatol Clin* 1990; 8: 747-50.
60. WRIGHT S. Essential fatty acids and atopic dermatitis. *Pediatr Allergy Immunol* 1991; 2 Suppl 1: 23-30.
61. COOPER KD. Pathogenesis and pharmacology of atopic dermatitis. In: CZERNIELEWSKI JM, ed. *Immunological and pharmacological aspects of atopic and contact eczema*. Pharmacology and the skin, Vol 4. Basel: Karger, 1991: 119-27.
62. CLARK RAF. Cell-mediated and IgE-mediated immune responses in atopic dermatitis [editorial]. *Arch Dermatol* 1989; 125: 413-16.
63. BRUYNZEEL-KOOMEN C, VAN WICHEN DF, TOONSTRA J, BERRENS L, BRUYNZEEL PLB. The presence of IgE-molecules on epidermal Langerhans cells in patients with atopic dermatitis. *Arch Dermatol Res* 1986; 278: 199-205.
64. BARKER JNWN, ALEGRE VA, MACDONALD DM. Surface-bound immunoglobulin E on antigen-presenting cells in cutaneous tissue of atopic dermatitis. *J Invest Dermatol* 1988; 90: 117-21.
65. BIEBER T, DANNENBERG B, PRINZ JC, et al. Occurrence of IgE-bearing epidermal Langerhans cells in atopic eczema: a study of the time course of the lesions and with regard to the IgE serum level. *J Invest Dermatol* 1989; 92: 215-19.
66. BIEBER T, RIEGER A, NEUCHRIST C, et al. Induction of FcεR2/CD23 on human epidermal Langerhans cells by human recombinant interleukin 4 and γ interferon. *J Exp Med* 1989; 170: 309-14.
67. FOKKENS WJ, BRUYNZEEL-KOOMEN CAFM, VROOM TM, et al. The Langerhans cell: an underestimated cell in atopic disease. *Clin Exp Allergy* 1990; 20: 627-38.
68. SAARINEN UM. Transfer of latent atopy by bone marrow transplantation? A case report. *J Allergy Clin Immunol* 1984; 74: 196-200.
69. PARKMAN R, RAPPEPORT J, GEHA R, et al. Complete correction of the Wiskott-Aldrich syndrome by allogeneic bone-marrow transplantation. *N Engl J Med* 1978; 298: 921-7.
70. SAURAT JH. Eczema in primary immune-deficiencies. *Acta Derm Venereol* (Stockh) 1985; 114: 125-8.
71. LEVER R, TURBITT M, SANDERSON A, MACKIE R. Immunophenotyping of the cutaneous infiltrate and of the mononuclear cells in the peripheral blood in patients with atopic dermatitis. *J Invest Dermatol* 1987; 89: 4-7.
72. MIHM MC, SOTER NA, DVORAK HF, AUSTEN KF. The structure of normal skin and the morphology of atopic eczema. *J Invest Dermatol* 1976; 67: 305-12.
73. IRANI AMA, SAMPSON HA, SCHWARTZ LB. Mast cells in atopic dermatitis. *Allergy* 1989; 44 Suppl 9: 31-4.
74. LEIFERMAN KM. Eosinophils in atopic dermatitis. *Allergy* 1989; 44 Suppl 9: 20-6.
75. JORDAN JM, WHITLOCK FA. Emotions and the skin: the conditioning of scratch responses in cases of atopic dermatitis. *Br J Dermatol* 1972; 86: 574-85.
76. WAHLGREN CF, HÄGERMARK Ö, BERGSTRÖM R. Patients' perception of itch induced by histamine, compound 48/80 and wool fibres in atopic dermatitis. *Acta Derm Venereol* (Stockh) 1991; 71: 488-94.
77. LEBEL B, VENENCIE PY, SAURAT JH, SOUBRANE C, PAUPE J. Anti-IgE induced histamine release from basophils in children with atopic dermatitis. *Acta Derm Venereol* (Stockh) 1980; Suppl 92: 57-9.
78. VON DER HELM D, RING J, DORSCH W. Comparison of histamine release and prostaglandin E2 production of human basophils in atopic and normal individuals. *Arch Dermatol Res* 1987; 279: 536-42.
79. WILLIAMS DH. Skin temperature reaction to histamine in atopic dermatitis (disseminated neurodermatitis). *J Invest Dermatol* 1938; 1: 119-29.
80. JOHNSON HH, DEOREO GA, LASCHIED WP, MITCHELL F. Skin histamine levels in chronic atopic dermatitis. *J Invest Dermatol* 1960; 34: 237-8.
81. JUHLIN L. Localization and content of histamine in normal and diseased skin. *Acta Derm Venereol* (Stockh) 1967; 47: 383-91.
82. RUZICKA T, GLÜCK S. Cutaneous histamine levels and histamine releasability from the skin in atopic dermatitis and hyper-IgE-syndrome. *Arch Dermatol Res* 1983; 275: 41-4.
83. RING J. Plasma histamine concentrations in atopic eczema. *Clin Allergy* 1983; 13: 545-52.
84. CORMIA FE, DOUGHERTY JW. Clinical evaluation of antipruritic drugs. *Arch Dermatol* 1959; 79: 172-8.
85. HURLEY HJ. Clinical techniques for evaluating antipruritic and topical dermatologic preparations. In: NODINE JH, SIEGLER PE, eds. *Animal and clinical pharmacologic techniques in drug evaluation*. Chicago: Year Book Medical Publ., 1964: 262-5.
86. EPSTEIN E, PINSKI JB. A blind study. *Arch Dermatol* 1964; 89: 548-9.
87. FISCHER RW. Comparison of antipruritic agents administered orally. *JAMA* 1968; 203: 418-19.
88. FROSC PJ, SCHWANITZ HJ, MACHER E. A double blind trial of H1 and H2 receptor antagonists in the treatment of atopic dermatitis. *Arch Dermatol Res* 1984; 276: 36-40.
89. SAVIN JA, DOW R, HARLOW BJ, MASSEY H, YEE KF. The effect of a new non-sedative H1-receptor antagonist (LN2974) on the itching and scratching of patients with atopic eczema. *Clin Exp Dermatol* 1986; 11: 600-2.
90. DOHERTY V, SYLVESTER DGH, KENNEDY CTO, HARVEY SG, CALTHROP JG, GIBSON JR. Treatment of itching in atopic eczema with antihistamines with a low sedative profile. *BMJ* 1989; 298: 96.
91. BERTH-JONES J, GRAHAM-BROWN RAC. Failure of terfenadine in relieving the pruritus of atopic dermatitis. *Br J Dermatol* 1989; 121: 635-7.
92. KRAUSE L, SHUSTER S. Mechanism of action of antipruritic drugs. *BMJ* 1983; 287: 1199-200.

93. TASAKA K, MIO M, OKAMOTO M. Intracellular calcium release induced by histamine releasers and its inhibition by some antiallergic drugs. *Ann Allergy* 1986; 56: 464–9.
94. KREUTNER W, CHAPMAN RW, GULBENKIAN A, SIEGEL MI. Antiallergic activity of loratadine, a non-sedating antihistamine. *Allergy* 1987; 42: 57–63.
95. LEPREVOST C, CAPRON M, DE VOS C, TOMASSINI M, CAPRON A. Inhibition of eosinophil chemotaxis by a new anti-allergic compound (cetirizine). *Int Arch Allergy Appl Immunol* 1988; 87: 9–13.
96. UEHARA M, IZUKURA R, SAWAI T. Blood eosinophilia in atopic dermatitis. *Clin Exp Dermatol* 1990; 15: 264–66.
97. WASSOM DL, LOEGERING DA, SOLLEY GO, et al. Elevated serum levels of the eosinophil granule major basic protein in patients with eosinophilia. *J Clin Invest* 1981; 67: 651–61.
98. JAKOB T, HERMANN K, RING J. Eosinophil cationic protein in atopic eczema. *Arch Dermatol Res* 1991; 283: 5–6.
99. BRUYNZEEL-KOONEN CAFM, VAN WICHEN DF, SPRY CJF, VENGE P, BRUYNZEEL PLB. Active participation of eosinophils in patch test reactions to inhalant allergens in patients with atopic dermatitis. *Br J Dermatol* 1988; 118: 229–38.
100. ZHEUTLIN LM, ACKERMAN SJ, GLEICH GJ, THOMAS LL. Stimulation of basophil and rat mast cell histamine release by eosinophil granule-derived cationic proteins. *J Immunol* 1984; 133: 2180–5.
101. LEIFERMAN KM, LOEGERING DA, GLEICH GJ. Production of wheal-and-flare skin reactions by eosinophil granule proteins [abstract]. *J Invest Dermatol* 1984; 82: 414.
102. REINHOLD U, KUKEL S, GOEDEN B, NEUMANN U, WEHRMANN W, KREYSEL HW. Interleukin-4 promotes the expansion of skin-infiltrating lymphocytes from atopic dermatitis in vitro. *J Invest Dermatol* 1991; 96: 370–5.
103. REINHOLD U, GOEDEN B, KUKEL S, NEUMANN U, WEHRMANN W, KREYSEL HW. *In vitro* expanded skin-infiltrating lymphocytes from atopic dermatitis lesions secrete high levels of interleukin-4 and low levels of interferon-gamma [abstract]. *Skin Pharmacol* 1991; 4: 38–9.
104. VAN DER HEIJDEN FL, WIERENGA EA, BOS JD, KAPSENBERG ML. High frequency of IL-4-producing CD4+ allergen-specific T lymphocytes in atopic dermatitis lesional skin. *J Invest Dermatol* 1991; 97: 389–94.
105. VAN DER HEYDEN FL, WIERENGA EA, BOS JD, KAPSENBERG ML. Atopic eczema skin-derived T cell clones: allergen specificity and cytokine production [abstract]. *Skin Pharmacol* 1991; 4: 39–40.
106. LIESCHKE GJ, MAHER D, CEBON J, et al. Effects of bacterially synthesized recombinant human granulocyte-macrophage colony-stimulating factor in patients with advanced malignancy. *Ann Intern Med* 1989; 110: 357–64.
107. KAPLAN G, KIESSLING R, TEKLEMARIAM S, et al. The reconstitution of cell-mediated immunity in the cutaneous lesions of lepromatous leprosy by recombinant interleukin 2. *J Exp Med* 1989; 169: 893–907.
108. GASPARI AA, LOTZE MT, ROSENBERG SA, STERN JB, KATZ SI. Dermatologic changes associated with interleukin 2 administration. *JAMA* 1987; 258: 1624–9.
109. WAHLGREN CF, TENGVALL LINDER M, SCHEYNIUS A. Effects of cyclosporin A in atopic dermatitis: expression in the skin of IgE, low-affinity Fc-IgE receptors, ICAM-1 and eosinophilic granulocytes. *Eur J Dermatol* 1992; 2: 112–8.
110. MUNRO CS, HIGGINS EM, MARKS JM, DALY BM, FRIEDMANN PS, SHUSTER S. Cyclosporin A in atopic dermatitis: therapeutic response is dissociated from effects on allergic reactions. *Br J Dermatol* 1991; 124: 43–8.
111. HIGGINS EM, MUNRO CM, REES J, et al. Effects of cyclosporin on physiological and pharmacological reactions in skin [abstract]. *J Invest Dermatol* 1988; 91: 397.
112. SHAW LM. Advances in cyclosporine pharmacology, measurement, and therapeutic monitoring. *Clin Chem* 1989; 35: 1299–308.
113. SHARPE RJ, ARNDT KA, BAUER SI, MAIONE TE. Cyclosporine inhibits basic fibroblast growth factor-driven proliferation of human endothelial cells and keratinocytes. *Arch Dermatol* 1989; 125: 1359–62.
114. MARONE G, TRIGGIANI M, CIRILLO R, GIACUMMO A, SIRI L, CONDORELLI M. Cyclosporin A inhibits the release of histamine and peptide leukotriene C4 from human lung mast cells. *Ricerc Clin Lab* 1988; 18: 53–9.
115. COWAN MA. Neurohistological changes in lichen simplex chronicus. *Arch Dermatol* 1964; 89: 562–8.
116. PINCELLI C, FANTINI F, MASSIMI P, GIROLOMONI G, SEIDENARI S, GIANETTI A. Neuropeptides in skin from patients with atopic dermatitis: an immunohistochemical study. *Br J Dermatol* 1990; 122: 745–50.
117. GIANNETTI A, GIROLOMONI G. Skin reactivity to neuropeptides in atopic dermatitis. *Br J Dermatol* 1989; 121: 681–8.
118. UEHARA M, MIYAUCHI H. The morphologic characteristics of dry skin in atopic dermatitis. *Arch Dermatol* 1984; 120: 1186–90.
119. MELNIK BC. Disturbances of epidermal lipid metabolism and barrier function in atopic eczema. In: RUZICKA T, RING J, PRZYBILLA B, eds. *Handbook of atopic eczema*. Berlin-Heidelberg: Springer-Verlag, 1991: 296–305.
120. WERNER Y, LINDBERG M. Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. *Acta Derm Venereol (Stockh)* 1985; 65: 102–5.
121. FJELLNER B, HÄGERMARK Ö. Pruritus in polycythemia vera: treatment with aspirin and possibility of platelet involvement. *Acta Derm Venereol (Stockh)* 1979; 59: 505–12.
122. HÄGERMARK Ö, RAJKA G, BERGQVIST U. Experimental itch in human skin elicited by rat mast cell chymase. *Acta Derm Venereol (Stockh)* 1972; 52: 125–8.
123. FJELLNER B, HÄGERMARK Ö. Studies on pruritogenic and histamine-releasing effects of some putative peptide neurotransmitters. *Acta Derm Venereol (Stockh)* 1981; 61: 245–50.
124. HÄGERMARK Ö, HÖKFELT T, PERNOW B. Flare and itch induced by substance P in human skin. *J Invest Dermatol* 1978; 71: 233–5.
125. CAMP RDR, COUTTS AA, GREAVES MW, KAY AB, WALPORT MJ. Responses of human skin to intradermal injection of leukotrienes C4, D4 and B4. *Br J Pharmacol* 1983; 80: 497–502.
126. FJELLNER B, HÄGERMARK Ö. Experimental pruritus evoked by platelet activating factor (PAF-acether) in human skin. *Acta Derm Venereol (Stockh)* 1985; 65: 409–12.