Abstract
Phototherapy is an efficacious method for managing many cutaneous conditions. Although psoriasis is the most commonly treated condition, phototherapy also has a role in the management of pruritic disorders, including atopic dermatitis (AD), prurigo nodularis (PN), and uremic pruritus (UP). We have reviewed the pathogenesis of pruritus and the mechanism of action of phototherapy in treating pruritic disorders. AD is an inflammatory skin condition with an induction of pruritus due to cytokines released by CD4-positive-T helper (Th) 2 cells. Langerhans cells, T cells, proinflammatory cytokines, and keratinocytes are decreased in AD patients treated with phototherapy. PN has an increase in mast cells and neuropeptides that mediate pruritus. UV light decreases the release of these neuropeptides and alleviates pruritus in PN. Finally, UP causes a microinflammatory state with changes in cutaneous nociceptive endings. A circulating substance responsible for pruritus in UP is annihilated through the apoptotic actions of phototherapy.

Introduction
Pruritus is the number one symptom presented to any dermatology practice. The physical and psychological distress caused by chronic pruritus has a significant impact on quality of life for patients. Because topical therapy is often inadequate in controlling pruritus, other treatments are needed. Phototherapy can alleviate the constant sensation of itch without many of the adverse effects of systemic medications. In addition, it is safe and can be utilized in all age categories. UVB (290-320 nm) and UVA (320-400 nm) are implemented in UV-based therapy. Broadband UVB (BB-UVB) and broadband UVA (BB-UVA) use a light source covering their entire spectrum. Narrowband UVB (NB-UVB) uses 311-313 nm, and UVA1 uses 340-400 nm with a peak at 365 nm. UVA1 can be administered at high dose (HD-UVA1) (130 J/cm²), medium dose (MD-UVA1) (50 J/cm²), and low dose (LD-UVA1) (20 J/cm²). Monochromatic excimer laser (MEL) (308nm) is a more targeted phototherapy device that delivers 308 nm UVB to a localized area and can expand treatment options by sparing unaffected areas. Both cutaneous and systemic diseases can present with pruritus as the primary symptom. This article summarizes the pathogenesis of pruritic disorders including AD, PN, and UP and the mechanism of action of phototherapy in each of these (Table 1).

Discussion
Pathogenesis of Itch: Localized itch involves alpha-delta fibers, whereas diffuse, generalized itch is transmitted through dermal unmyelinated c-fibers. Both of these nociceptive fibers travel to the dorsal horn of the spinal cord, which is then processed by the cerebral cortex through the spinothalamic tract. They have a slow conduction velocity and innervate large areas of the skin. Dry skin and disruption of the skin barrier can induce keratinocytes to release pruritogenic substances. Nerve fibers typically end at the dermal-epidermal junction, although some project into the epidermis. Itch receptors, formed mostly by keratinocytes, respond to...
pruritogens such as histamine, proteases, growth factors, neuropeptides, cytokines, and opioids (Figure 1). They are found only in skin, mucus membranes, and cornea. Substance P (SubP) and calcitonin gene-related peptide (CGRP) are the most studied neurotransmitters and have both central and peripheral activity. Allokinesis, the perception of non-pruritic stimuli as pruritic, is due to central sensitization. This explains the intense pruritis AD patients experience in response to sweat or sudden changes in ambient temperature.

Mast cells produce two proteinases, tryptase and chymase. Tryptase activates C fibers and thus stimulates the sensation of itch. It also triggers the release of SubP, which not only causes pruritis but also evokes further mast-cell activation. Increased levels of tryptase have been observed in patients with UP.

The sensations of pain and itch are carried by different C-fibers. Frequency of the stimulus can modulate the magnitude of itch but does not change the quality of itch into pain. Histamine-induced itch activates some motor areas, suggesting a neuronal association between itch and scratching. Scratching and vibration are transmitted by larger A-beta fibers that inhibit itch signals on the slower C-fibers. While pain causes one to avoid a motor response, itch causes a stimulatory motor response. Painful stimuli can inhibit itch, as observed in pruritic patients who only stop scratching once skin lesions begin bleeding and become painful. Itch and pain share the same cortical brain areas but have different patterns of activation: Itch has a weaker activation of somatosensory cortices and a stronger activation of ipsilateral motor areas as compared with pain processing.

**ATOPIC DERMATITIS (AD)**

Pathogenesis of AD: The pathogenesis of AD is a complex interplay between several different cell types and factors. CD-4 positive Th2 cells have been found to play a major role in pruritus induction by producing and releasing cytokines and chemokines. Localization to the skin in AD is due to the presence of a skin-homing receptor on memory effector T lymphocytes, called "cutaneous lymphocyte-associated antigen," which interacts with the vascular endothelial-cell-surface antigens to direct circulating T lymphocytes to the reactive skin site. Th1 cells initiated by IL-12 predominantly secrete IL-2 and interferon-\(\gamma\) (IFN-\(\gamma\)), whereas Th2 cells are activated by IL-10 to produce mainly IL-4, IL-5, and IL-13. 24

Atopic disorders such as eczema have been associated with a hyper Th2 response, as they signal B lymphocytes to produce IgE, stimulate eosinophils and mast cells, and cause type 1 hypersensitivity reactions. Environmental factors may enhance Th2 allergic response. AD patients commonly have a higher *Staphylococcus aureus* burden than the general population, and the Th2 cytokines of AD augment the toxicity of the lytic staphylococcal protein alpha toxin. It has been shown that, although the initiation of eczematous lesions is a Th2-driven response, chronic lesions demonstrate a greater level of Th1 activity. Acute and chronic AD lesions contain more mRNA expression for IL-4, IL-5, and IL-13 than normal skin. The mRNA expression of IFN-\(\gamma\), however, is similar to that of normal skin. Chronic lesions express more IL-5, IL-12 and anti-cosinophil cationic protein (ECP) antibody eosinophils than acute lesions. Thus, IL-12 may be important in the transition from acute to chronic lesions. The predominance of Th2 cytokines in the acute phase, such as IL-4 and IL-5, stimulates eosinophils, which produce IL-12, thereby activating Th1 cells and undifferentiated T cells to produce IFN-\(\gamma\), causing a negative feedback on Th2 responses and maintaining the AD lesion over an extended period (Figure 2).

The stratum corneum is the permeability barrier between the body and the external environment, and thus when it is impaired, increased transdermal water loss causes xerosis and intense pruritus. The barrier is compromised due to an overexpression of an enzyme that hydrolyzes sphingomyelin, producing free fatty acid and sphingosylphosphorylcholine, an inducer of keratinocyte proliferation and up-regulator of plasminogen activator, resulting in decreased ceramides. Additionally, scratching from pruritus induces trauma and further insult to an already compromised stratum corneum, which triggers keratinocytes to release proinflammatory cytokines. It is also because of this defective barrier that microorganisms such as *S. aureus* enter and colonize eczematous skin. Toxins released by microbes further interfere with ceramide metabolism, as cytolytic alpha toxin causes keratinocyte damage and superantigenic toxin causes release of TNF-alpha and Beta-hemolysin, which interfere with ceramide metabolism. These toxins also prevent keratinocytes from producing antimicrobial peptides to kill *S. aureus*.

**Mechanism of Action for Phototherapy in AD:** Many studies have demonstrated the beneficial effects of phototherapy in treating AD. The intraleisonal mRNA expression of IFN-\(\gamma\) was successfully downregulated during the course of UVA1 therapy, whereas IL-4 mRNA expression remained relatively unchanged even after those with chronic AD improved under treatment. The high efficacy of UVA1 phototherapy in the treatment of AD can be attributed to the combination of UV-light induced apoptosis of T lymphocytes as well as the reduction of Langerhans cells and mast cells in the dermis. Preventing Langerhans cells and mast cells from exiting the epidermis results in a decreased number of Ig-E binding cells in the dermis. Phototherapy induces the immunosuppressive mechanisms of the body, such as suppressing the antigen-presenting function of Langerhans cells, inducing apoptosis in infiltrating T cells, causing DNA damage, and halting the rapid accumulation of epidermal keratinocytes.

Colonization by *Staphylococcus aureus* and *Pityrosporum orbiculare* is decreased through the use of UV radiation. UV light also increases the thickness of the stratum corneum and therefore results in smaller eczematous reactions due to a decreased penetration of antigens. Thus, UV light exerts...
its beneficial effects through a multitude of mechanisms. Although AD is the primary disease explained above, a similar mechanism of action for UV-based therapy can be applied to PN and LSC owing to their similar inflammatory nature.

**PRURIGO NODULARIS (PN)**

**Pathogenesis of PN:** A background of atopic diathesis has been suggested for PN after examining the history of AD, allergic rhinitis, and bronchial asthma.\(^4\) Tanaka et al. found examining the history of AD, allergic rhinitis, diathesis has been suggested for PN after A background of atopic Pathogenesis of PN:

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**Histopathologically, PN has an increased downward projection of the epidermis, suggesting pseudoepitheliomatous hyperplasia.** Skin biopsies of PN reveal an increase in the number of mast cells in both the epidermis and the dermis, with some invasion into the cutaneous nerve-fiber bundles.\(^3\) Mast cells are known to release nerve growth factor (NGF) and are seen in proximity to nerves expressing increased levels of NGF receptor (NGFr) (**Figure 3**).\(^1,2\) Thus, the overexpression of NGF in PN explains the neurohyperplasia, which subsequently explains the strong itch secondary to increased axon firing.\(^3\) The mast cells in PN lesions also demonstrate morphological changes, such as enlarged cell bodies with a dendritic shape as compared to the round shape seen in normal skin.\(^3,5,6\) Thus, neuropeptides and histamine from mast cells cooperatively generate neurogenic inflammation to induce and transmit itch. Eosinophils can also release NGF and contribute to neurohyperplasia of PN.\(^5\) Dermal Langerhans cells are increased in PN, suggesting their involvement in the development or persistence of PN.\(^7\) In addition, the numbers of Merkel cells are increased in PN at the basal cell layer, explaining the abnormal sensitivity to touch from these slowly adapting sensory touch receptors.\(^8\)

**Mechanism of Action for Phototherapy in PN:** UV light hinders rapid epidermal cell turnover and thereby leads to a reduction in pseudoepitheliomatous hyperplasia of the epidermis.\(^9\) PN patients have an increase in the number of nerve fibers in the papillary dermis.\(^10\) These nerve fibers demonstrate immunoreactivity for SubP and CGRP and thus mediate the cutaneous neurogenic inflammation and pruritus in PN. It is postulated that MEL modulates the release of these neuropeptides.\(^11-13\) The long remission noted for MEL could be due to inhibition of neuropeptide releases, which cause pruritus and can consequently perpetuate the rubbing, scratching, and picking cycle. MEL treatment causes a depletion of T cells and alterations of apoptosis-related molecules, along with a decreased proliferation index of keratinocytes.\(^14\) PUVA downregulates CGRP and Th2 cytokines and depletes epidermal dendritic cells.\(^15,16\) The longer wavelengths used in PUVA penetrate the acanthotic thick epidermis more fully than classical NB-UVB.\(^17-19\) UVB irradiation inhibits mast-cell granule release.\(^20\) Thus, phototherapy is successful in combating itch in PN because it reduces the number of epidermal nerve fibers.\(^6\)

UVB therapy is beneficial for patients with UP. Possible mechanisms include reduction in skin divergent ion content, reduction in Vitamin A and retinol content, stabilization of or reduction in number of mast cells, detoxification of undetermined pruritogen substances, photoactivation of antipruritogenic substances, and changes in the excitability of epidermal nerve endings. Mast-cell proliferation, degranulation, and subsequent histamine release plays a role in uremic pruritus (**Figure 4**). Histamine secretion is evoked by an increased release of SubP.\(^21\) NB-UVB induces apoptosis of dermal mast cells and reduces the release of neuropeptides such as SubP by decreasing epidermal nerve fibers.\(^22-24\) Nitric oxide and IL-2 have also been implicated in the pathogenesis of uremic pruritus, both of which are decreased by NB-UVB.\(^25-28\) Schultz et al. suggest the response to UVB indicates a deposition of some substance in the skin that is degraded or inactivated by the light. Because uremic patients respond to cholestyramine, and phototherapy serves to clear bilirubin in jaundiced premature infants, bile salts were considered to be involved in UP pathogenesis.\(^29\) Individuals with advanced CRF had higher levels of serum total bile acids when compared to controls, and those with pruritus had higher levels of bile acids than those without pruritus. Thus, the intensity of pruritus correlated with bile acid concentration.\(^30\) Certain bile acids also cause cytotoxicity to mastocytes, thereby releasing histamine.\(^31\)
Table 1: Comparison of Mechanism of Action of Phototherapy in Pruritic Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of Phototherapy</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Atopic Dermatitis</td>
<td>UVA1</td>
<td>↓IFN – gamma&lt;br&gt;↑T cells&lt;br&gt;↑Langerhans cells&lt;br&gt;↓Mast cells&lt;br&gt;↑IgE binding&lt;br&gt;↓colonization by Staphylococcus aureus and Pityrosporum orbiculare&lt;br&gt;↑Stratum corneum thickness</td>
</tr>
<tr>
<td>Prurigo Nodularis</td>
<td>MEL</td>
<td>↓epidermal cell turnover&lt;br&gt;↓neuropeptide release&lt;br&gt;↑T cells</td>
</tr>
<tr>
<td>Prurigo Nodularis</td>
<td>PUVA</td>
<td>↓CGRP&lt;br&gt;↑Th2 cytokines&lt;br&gt;↑Dendritic cells</td>
</tr>
<tr>
<td>Uremic Pruritus</td>
<td>UVB</td>
<td>↓Skin-divalent ions&lt;br&gt;↓Vitamin A and Retinols&lt;br&gt;↑Mast cells&lt;br&gt;↑SubP&lt;br&gt;↑Nitric oxide&lt;br&gt;↑IL-2&lt;br&gt;↑Antipruriticogenic substances</td>
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Conclusion

The mechanisms of action for phototherapy in each of the discussed pruritic disorders are unique and dependent on the pathophysiology of the disease. Phototherapy decreases pruritus in AD, PN, and UP through its apoptotic and anti-inflammatory actions and is therefore a useful therapeutic modality for these disorders. Due to the similarity in mechanisms of these diseases, there is sufficient evidence to support the use of various forms of UB-based treatment for reducing pruritus and its associated manifestations.

References


64. Bianchi B, Campolmi P, Mavilia L, Danesi A, Rossi AP, Gelfand EW, Leung DY. Preferential binding of Do15.soham.chaudhari@nv.touro.edu

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