Pruritus: A Review

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The history, neurophysiology, clinical aspects and treatment of pruritus are reviewed in this article. The different forms of pruritus in dermatological and systemic diseases are described, and the various aetiologies and pathophysiology of pruritus in systemic diseases are discussed. Lack of understanding of the neurophysiology and pathophysiology of pruritus has hampered the development of adequate therapies. Nevertheless, the discovery of primary afferent neurons and, presumably, second-order neurons with typical histamine responses mediating pruritic sensations can be regarded as a breakthrough in our understanding of the mechanisms behind pruritus. The number of experimental and therapeutic studies has greatly increased during the past few years, reflecting an increased interest in this topic. However, further effort is needed to develop new therapeutic concepts and clarify some confusion arising from promising case reports and uncontrolled clinical studies. A precise work-up for evaluating patients with pruritus is proposed, which may help the physician to identify the underlying causes and thus to treat the patient appropriately. *Key words: itch; mediators of itch; neurophysiology; sensation; skin*

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INTRODUCTION

Pruritus can be defined subjectively as a poorly localized, non-adapting, usually unpleasant sensation that provokes a desire to scratch. The biological purpose of pruritus is to induce scratching in order to remove a pruritogen – a response likely to have originated when most pruritogens were parasites.

Pruritus is the most frequently described symptom in dermatology. It can arise from a primary dermatologic aetiology, but in an estimated 10–50% of patients it may also be a symptom of underlying systemic disease (1, 2). Differential diagnoses include metabolic disorders, haematologic disease, malignancy, HIV/AIDS, complications of pharmacologic therapy and neuropsychiatric disorders. It could be considered that there are systemic or central aspects of pruritus in dermatological diseases and of course that there are dermatological factors causing pruritus in systemic diseases. Pruritus can also occur without visible skin symptoms (3), and in systemic diseases can result from a specific dermatological disease or infiltrate directly related to the underlying disease, e.g. cutaneous infiltrates in Hodgkin's disease. This always needs to be considered in the setting of pruritus in systemic diseases and has to be ruled out by the experienced dermatologist using the necessary diagnostic tools, e.g. skin biopsy. Pruritus may also occur in dermatological and systemic diseases not directly related to specific dermatoses or infiltrates.

Severe pruritus usually leads to secondary lesions such as erythema, erosions, excoriations and crusts, followed by cutaneous infections that can result in folliculitis, abscess or erysipelas. The overall incidence and prevalence of pruritus remains unknown for several reasons: *(i)* there are no epidemiologic databases for this entity, *(ii)* many studies do not record pruritus as a symptom, especially in non-dermatologic fields, and *(iii)* few people present to a physician for minor pruritic conditions. However, it is reasonable to assume that everyone experiences this sensation at some point in life.

When a patient complains of pruritus there is a rational way to assemble the myriad of aetiologies into finite groups so that the patient can be evaluated in a thoughtful manner, the underlying cause corrected and the pruritus treated with currently available therapies.

History of pruritus

The first mentions of pruritus are found in the Bible: "If, however, in his judgment it is unchanged and black hair has grown in it, the itch is healed. He is clean, and the priest shall pronounce him clean" (Leviticus 13: 36–38). In Deuteronomy (28: 26–28), it is stated that "the Lord will afflict you with the boils of Egypt and with tumours, fleeting sores and the itch, from which you cannot be cured".

Hippocrates of Cos (460–377 BC) described pruritus vulvae, senile pruritus and prurigo, the latter as a disfigurement rather than a disease (4). The definition of pruritus as an unpleasant sensation that provokes the desire to scratch was introduced in 1660 by the German physician Samuel Hafenreffer (5).

In dealing with the history of pruritus the focus has to be on a physician, and in this case one of the most impressive and radical leaders of the French revolution, Jean Paul Marat. The exact date of onset and diagnosis of his skin disease is a matter of speculation, but during his last years in particular he would spend most of the day in a medical bath seeking relief from persistent pruritus and vigorous scratching while writing and editing his newspaper (6–8). He was assassinated in 1793 by a counter-revolutionary as he sat in his bath. It is hypothesized that Marat's skin disease caused him to be seen as a leper, to identify with social outcasts, and therefore to ally himself with the Parisian poor (9). With time, the tone of his speeches became more and more radical and violent, probably in relation to the increasing severity of his pruritus. These circumstances prompt the question whether Marat's skin disease and pruritus could have affected history (9).

History of pruritus as an investigative topic is rather poor. In 1994, after a century of research in dermatology, it was said that no progress had been made in understanding, let alone relieving, pruritus (10). To a great extent, this is still the case today. Though recent experimental findings have yielded deeper insights into the pathophysiology of pruritus (11, 12), many aspects of neurophysiology and pathogenesis remain unclear, including the neuromechanisms involved in pruritus accompanying inflammatory skin disease.

NEUROPHYSIOLOGY

Basic mechanisms

Neurons can be categorized as either myelinated or unmyelinated. The former divide into rapidly conducting (A-β) and slowly conducting (A-Δ) fibres. It is the coating of myelinated fibres that allows action potentials to travel at a greater speed compared to unmyelinated fibres. Conducting velocity is a useful tool for classifying the function of sensory neurons because it does not overlap in myelinated and unmyelinated fibres. The most rapidly conducting ones are mechanoreceptive. Neurons that signal pain and irritation exist in both the myelinated and unmyelinated populations, and have been given the name 'nociceptors' to indicate their responsiveness to noxious stimuli. Human psycho-physiological studies have shown that the painful sensation evoked by activating myelinated neurons is different in quality (e.g. stinging, pricking) from the dull, aching pain evoked by the recruitment of unmyelinated neurons (1). Nociceptive neurons can be activated by mechanical, thermal and chemical stimuli. They can be subgrouped on the basis of conducting velocity, mechanical threshold, responsiveness to thermal stimuli and activation by specific chemicals. Their individual responsiveness differs: some respond to single stimuli only, others to several stimuli.

In 1959, it was shown for the first time using methylene blue stain that the intraepidermal nerve fibres branch and ascend closely underneath the stratum corneum (13). This was later confirmed by light microscopy with the recent advances in immunohistochemistry and silver impregnation (14–17). As recently reported, intraepidermal nerve fibres might not be distributed evenly in the hairy portions of normal human skin; they can be present focally, with the greater distribution in the arm, followed by the face, the legs and abdomen (18). The "two-point discrimination" of pruritus reflects the ability to perceive two pruritic stimuli as separate. This is better in patients with atopic dermatitis (AD) than in healthy controls (19). The main determinant of the measure is the innervation territory of one neuron. The lower innervation density of pruritic nociceptors and/or different central processing of pruritus might account for the reduced sensitivity to histamine-induced experimental pruritus of the scalp (20).

The neural representation of pruritus is not fully understood and is therefore controversial. For many years, pruritus has been considered a sublimal form of pain, because it is abolished along with pain and temperature sensations when the lateral spinothalamic tract is interrupted by cordiotomies. On the one hand, both sensations share common features; they are multidimensional, they are induced by chemical stimuli and they initiate motor response and negative affective valence. It is well known that opioids reduce pain but may induce pruritus, which can be strongly inhibited by noxious stimuli. On the other hand, pruritic sensations cannot be transformed to pain, and micro-stimulation of fascicles that evoke pain cannot produce pruritus. In summary, pain and pruritus are probably two distinct sensations that interact.

The sensation of pruritus arises from the superficial layers of the skin and the mucous membranes. Itch receptors are free unmyelinated nerve endings (C-fibres) occurring in the epidermis of the skin and the mucous membrane. In 1997, a new class of afferent nerve fibres with particularly thin axons, excessive terminal branching, very low conduction velocities and histamine responsiveness was detected by microneurography in human beings (21). Interestingly, these C-units had a large innervation territory extending to 85 mm on the lower leg. The findings indicate that pruritus can be subserved by these specific primary afferent C-fibres (21). More recently, a class of spinothalamic tract neurons selectively excited by histamine was found in cats (12). As these neurons have distinct central conduction velocities and thalamic projections, they form a unique subset of spinothalamic tract neurons. Generally, no particularly good animal model exists for studies on pruritus (1). Species differences must be taken into account when models of pruritus are used (11, 12). In

summary, the second-order neurons found by Andrew & Craig (12) and the identification of primary afferent neurons with similar properties by Schmelz et al. (11, 21) can be regarded as a breakthrough in our understanding of the neurophysiological mechanisms of pruritus.

Central processing

Pruritic stimuli enter the central nervous system (CNS) via unmyelinated C-fibres and possibly A-Δ fibres. The axon enters through the dorsal horn for spinal dermatomes or the trigeminal equivalent of the brainstem for head and neck pruritus. After synaptic connection within the ipsilateral grey column of the spinal cord, processing and control of the transmission occur prior to crossing the midline. After synaptic transmission with the next neuron, the fibre ascends within the contralateral spinothalamic tract (22).

Although most of the peripheral pathways of pruritus (unmyelinated C-fibres) have been identified, they are still under investigation, and little is known about the central nervous processing of pruritus and scratching. The so-called "pruritus centre" has long been proposed as being at the medulla oblongata (1). Recent results obtained by positron emission tomography measuring regional cerebral blood flow (rCBF) as an index of neuronal activity revealed activation of cortical structures such as anterior cingulate cortex, supplementary motor area (SMA), premotor area (PM) and inferior parietal lobule, thereby substantiating that the posterior sector of the anterior cingulate cortex (Brodman 24) is related to sensorial/affectional aspects of the event (23). The premotoral cortical areas (SMA, PM) may participate in the preparation of an intended action. Another study demonstrated significant activation of the contralateral primary sensory cortex and the ipsilateral and contralateral motor areas (SMA, premotor cortex, primary motor cortex) (24). Additional significant activation was found in the prefrontal cortex and the cingulate gyrus. Several cortical areas reflect a graded increase in rCBF with the logarithm of the histamine concentration applied by prick testing. Pruritus and pain seem to share common pathways, but in contrast to pain activation studies, no subcortical activations were detected (24).

The phenomenon of alloknesis (allos=different, knesis=pruritus) was first described by Bickford in 1938 and designates a state when a normally non-pruritic stimulus induces pruritus in the skin surrounding a local cutaneous injury, e.g. an insect bite (25). It appears clinically as pruritus induced by touching the site of an insect bite that may have occurred several hours previously. In many pruritic dermatological diseases such as AD, alloknesis is observed when pruritic attacks occur after affected skin lesions, and/or the surrounding areas, are touched accidentally or are induced by mechanical factors such as clothing. Experimentally, alloknesis can be induced by mechanical stimuli, e.g. a soft brush or a cotton swab being stroked along the skin surrounding a histamine stimulus, and is considered an important tool in psycho-physical studies on pruritus (26–32). In analogy with the explanation of allodynia (= induction of pain by a usually non-painful stimulus), alloknesis is explained by the excitation of pruritus-mediating central neurons through interneurons receiving input from low-threshold, fast-conducting mechanoreceptor units gated by histamine-induced input from unmyelinated pruritus mediating nerve fibres (33, 34). Central and peripheral mechanisms probably contribute to the phenomenon of alloknesis. In two studies, the opiate antagonist naltrexone greatly reduced alloknesis, whereas the H_1 blocker cetirizine did not (27, 35). These results indicate a predominantly central effect of naltrexone compared to a predominantly peripheral effect of cetirizine (27). Another study showed that application of a topical agent, regardless of the active ingredient, abolishes or greatly reduces alloknesis, which is most likely due to the diminished excitation of mechanoreceptive fibres (29).

Atmoknesis (atmos=air, knesis=pruritus) is pruritus provoked by open exposure of the skin after undressing. It is common in AD, especially in children, psoriasis and elderly patients with aquagenic pruritus (36). Whether air itself really causes pruritus is unclear (36). Atmoknesis might be a consequence of skin temperature changes induced by draughts of air after undressing or is due to the mechanical stimuli of clothing while undressing and is in that way some type of alloknesis.

MEDIATORS OF PRURITUS

Mediators of pruritus presumably act on nerve fibres or lead to a cascade of mediator release whose final common pathway results in nerve stimulation and the sensation of pruritus. For example, vasoactive inflammatory mediators released during inflammation exert a dual action on nociceptive structures and on blood vessels. Activation of nociceptors leads to a release of neuropeptides that induce vasodilatation and protein extravasation in the skin; this has been termed "neurogenic inflammation" (37). It has been assumed that mast cell activation plays a role in dermal neurogenic inflammation, but, as recently demonstrated, dermal neurogenic inflammation does not degranulate mast cells (38).

The group of potential chemical mediators is large and is steadily increasing. It contains amines (e.g. histamine, serotonin), proteases (e.g. tryptases), neuropeptides (e.g. substance P (SP), calcitonin gene-related peptide (CGRP), bradykinin), opioids (morphine, beta-, met-, leu-enkephalin), eicosanoids, growth factors and cytokines (1). The major mediators are briefly reviewed below.

Histamine

Histamine is released during mast cell depletion and mediates its effects via H1 receptors in the skin (H_2 and H_3 receptors have not been described in the skin). Its effects, from either mast cell degranulation or intracutaneous injection, include the triple response (39): *(i)* localized red spot around the injection site as a consequence of local dilatation of capillaries, venules and terminal arterioles; *(ii)* red flush or flare extending around the red spot as a result of widespread dilatation of arterioles mediated by local axon reflex; *(iii)* wheal reduction due to histamine-induced permeability.

Histamine plays a major part in pruritus of urticaria and mastocytosis. Its mediation in pruritus of other pruritic states and diseases is suspect, and best proven by a poor clinical response to antihistamines in patients with pruritus who do not have urticaria. Besides, few pruritic diseases (except urticaria) are accompanied by wheals and flares. Furthermore, experimentally histamine-induced wheals and flares will usually only persist for up to 60 min, whereas pruritus in a disease state may last for hours and days.

As histamine is released by mast cell depletion, it may have a secondary role in diseases in which other mediators induce mast cell depletion or the total number of mast cells is enhanced. In haemodialysis-related pruritus, for example, increased numbers of mast cells and histamine levels have been detected, yet antihistamine showed only a marginal antipruritic effect (also see section 6 "Uremic/Renal Pruritus"). In one recent microdialysis study it was demonstrated that mast cell mediators other than histamine can cause pruritus in patients with AD (40).

Serotonin

Serotonin is less potent than histamine in inducing pruritus (32, 41, 42). In animal models and humans it most likely acts histamine-independently (32, 42). A mixture of prostaglandins and serotonin produces pruritus that can be relieved by aspirin (43). Serotonin is a potent activator of unmyelinated C-fibres (44). Its potency in inducing protein extravasation is low, however, and its differential effect on nociceptors and vasculature is best explained by a weak direct or indirect non-neurogenic effect on the endothelia – an effect which might be due to lower receptor density or affinity of the vasculature (45).

Neuropeptides

Over 50 described neuropeptides in the CNS and unmyelinated nerve fibres have been identified (46). Of these, SP and CGRP are the most frequently investigated in the skin. Their effects cover a wide range, such as acute proinflammatory reactions including vasodilatation and protein extravasation (47), trophic function and immuno-modulation (48).

SP is a peptide that is synthesized in dorsal root ganglia of nociceptive C-fibres and terminals and is transported peripherally to the nerve endings and released upon activation. It induces flare reactions by releasing histamine from mast cells by an indirect effect, and induces protein extravasation by a direct effect on small skin blood vessels and by a secondary release of histamine from mast cells (49). As recent data have demonstrated, SP is also capable of inducing histamine-independent vasodilatation and protein extravasation (50). In one study, SP and CGRP induced marked vasodilatation but did not induce pruritus or pain, even in much higher concentrations above the vasodilatory threshold (51). These findings suggest that vasoactive concentrations of SP and CGRP do not excite nociceptors and that they have no acute sensory function (50). They also contradict other results showing that dermal neuropeptides are transmitters of pruritus (51–54). All in all, the role of neuropeptides in protein extravasation, in mast cell activation, and its mediator function of pruritus, is not clear.

Opioids

Morphine induces histamine release from mast cells but does not lead to a triple response (1). Besides, opioid peptides appear to be involved in the central transmission and regulation of pruritus, but it is still not known in which central or peripheral structure opiate receptors could be involved. Recently, the μ-opioid receptor isoform 1A could be localized by immunohistochemistry on nerve fibres of human skin, which may contribute to neurogenic inflammation, pain and pruritus sensations (55).

Effects were seen in animals when central application of opiates led to scratching (56, 57). When plasma from patients with cholestatic pruritus was introduced in the medullary dorsal horn of monkeys, facial scratching was observed which was abolished by the opiate receptor antagonist naloxone (58). In human beings, intrathecal injection of morphine in particular may induce intense pruritus without skin lesions. Antihistamines do not prevent or relieve morphine-induced pruritus, which often occurs after 3–7 h. It is dose-related and typically spreads out from the injection site to the trunk, to the face (distribution of the trigeminal nerve) and/or to the whole body, but can also occur as facial pruritus only (59, 60). Its incidence is particularly high in caesarean delivery (61, 62). Morphine-induced pruritus usually subsides after cessation of the treatment. Naloxone is effective, but may carry the risk of decreasing the pain threshold (60). These observations suggest that the μ-opioid receptor system is involved in the processing of pruritus. Little is known about the role of the k-opioid receptor. TRK-820, a recently developed

k-opioid receptor agonist, did suppress antihistamine-sensitive and antihistamine-resistant pruritus in an experimental animal model (63). Further studies will show whether this is a new entity of drugs for treating pruritus in humans.

Elevated serum endorphin levels have been found in patients with AD (64). Though these have been reported as being accumulated in patients with hepatic impairment (1), this cannot be confirmed for renal pruritus (65). The role of serum endorphin levels in hepatic/cholestatic pruritus has not yet been completely clarified (66). One component of the pathophysiology of the syndrome of cholestasis is the increased CNS neurotransmission mediated by endogenous opioid agonists. Animal studies have recently highlighted loperamide, a peripherally acting opioid that was efficacious in models of pruritus and pain (67).

Cytokines

In various dermatological diseases pruritus is due to activation of cytokines and lymphokines such as in AD, autoimmune blistering diseases, allergic contact dermatitis, mycological and viral diseases (46). When patients with AD are treated with cyclosporin A that inhibits cytokines, pruritus, skin lesions and peripheral eosinophilia are significantly reduced (68). On the other hand, pruritus and inflammatory skin changes have been reported as side effects of cytokine treatment (69), such as in interleukin-2 (IL-2) treatment in cancer patients where pruritus and redness, dermal T-lymphocyte infiltrate and peripheral eosinophilia occur some days after initiation of the treatment (70). In patients with AD and controls, IL-2 induced a low intensity intermittent local pruritus that appeared after a few hours' delay and peaked between 6 h and 48 h (71). In another study investigating controls, a weak but significant early pruritogenic effect with no detectable axonic reflex was seen, and in this setting TNF-α did not induce pruritus (72). Others have shown that peripheral blood mononuclear cells of patients with AD can be stimulated to secrete IL-8 after antigen stimulation, but no measurable quantities of IL-2 and TNF-α were measured (73). It has been suggested that renal pruritus might be conveyed by, if not originate from, a deranged cytokine pattern with a pronounced pro-inflammatory profile (74). Cytokines could play a role in pruritus, but more research regarding their involvement in the pathomechanisms of pruritus is needed.

In summary, pruritus is most likely due to several mediators functioning together in the sense of an antagonistic effect and/or leading to mast cell depletion and the release of various substances including chymase, tryptase, interleukin-4 and histamine. Each cascade or predominating mediator may differ in each type of pruritus depending on the underlying disease.

EVALUATION OF THE PATIENT

History

A precise history provides insight into the disease process. Important characteristics of pruritus are given in Table I. Its onset, duration and nature help to determine the cause, and if some general clues are present the clinician will be able to narrow down the diagnosis:

- Localized pruritus is usually not a consequence of a systemic disease.
- Acute onset of pruritus without primary skin lesions over only a few days is less suggestive of an underlying systemic disease than chronic, progressive generalized pruritus.
- Secondary lesions on the upper mid-back suggest that a skin disease is responsible for the symptom, whereas sparing is associated with systemic causes of pruritus, representing the so-called "butterfly sign" due to the inaccessibility from the patient's hand.
- Most patients with pruritus not related to a primary dermatological disease demonstrate only excoriations or other secondary changes.
- Severely pruritic dermatoses, such as urticaria and mastocytosis, rarely lead to scratching and secondary

Table I. *Descriptive and historical features of pruritus*

Descriptive features of pruritus
1. Onset – e.g. abrupt, gradual, prior history of pruritic episodes
2. Time course – e.g. continuous, intermittent, cyclical, night-time
3. Nature – e.g. prickling, crawling, burning, dysaesthesia
4. Duration – e.g. days, weeks, months, years
5. Severity – e.g. interference with normal activities, night-time
6. Location – e.g. generalized or localized, unilateral or bilateral
7. Relationship to activities – e.g. occupational, hobbies
8. Provoking factors – e.g. water, skin cooling, air, exercise
9. Patient's personal theory as to aetiology of the disease'

Historical features of pruritus
1. Medications and topicals – prescribed, over the counter, illicit, duration and onset
2. Allergies – systemic, topical
3. Atopic history – eczema, allergic rhinitis and asthma
4. Past medical history – thyroid, liver, renal or other systemic diseases
5. Family history of atopy or skin disease or similar pruritic conditions
6. Occupation
7. Hobbies
8. Social history – household, personal contacts, food habits, stress
9. Drugs – nicotine, alcohol, i.v. drugs
10. Bathing habits, use of cosmetics
11. Pets and their care
12. Sexual history
13. Travel history
14. Prior diagnosis made by physician or patient

lesions, but instead involve pressing and rubbing behaviour.

- When multiple family members are affected, scabies or other parasites should be considered.
- Seasonal pruritus frequently occurs as "winter itch" representing pruritus in the elderly.
- The relationship between pruritus and physical activity is important. In association with physical activity, pruritus may resemble the cholinergic form. Pruritus provoked by the skin cooling after emerging from a bath may be a sign of polycythaemia rubra vera or idiopathic aquagenic pruritus.
- Nocturnal generalized pruritus in association with chills, sweating and fever may be a presenting history for Hodgkin's disease. Pruritus may precede onset of the disease by 5 years (75).
- Whereas psychogenic pruritus rarely interferes with sleep, most pruritic diseases (with or without primary skin lesions) cause nocturnal wakening.

Examination

Careful and complete examination of the skin, scalp, hair, nails, mucous membranes and the anogenital area is necessary. Evaluation of primary and secondary lesions, morphology, distribution, lichenification, xerosis and skin signs of systemic diseases must be performed. The general physical examination of lymph nodes, liver, spleen, etc., may disclose an undiagnosed systemic disease and has to be performed carefully when the differential diagnosis includes systemic disease and malignancy.

Laboratory investigation

There is no general need for laboratory investigation. However, in the setting of generalized pruritus of unknown aetiology, further investigation may be pursued (Table II). A skin biopsy including direct immunofluorescence may provide information in presentations where the pruritic skin is otherwise normal in appearance (Table III). On occasion, histologic examination of a non-specific secondary lesion could point to a specific dermatological disease.

Measuring pruritus severity and scratching

As a subjective symptom that cannot be verified by physical or biophysical examination, measuring the severity of pruritus is a challenge. Several modalities have been proposed to aide the clinician.

Categorical scales are the most commonly employed research scales and consist of discrete divisions of the frequency of the measured dimension. They can also be employed to assess the impact of pruritus on the life of the affected patient (46). Examples: pruritus – never, rarely, occasionally, frequently, always.

Interval scales describe pruritus by a number on a fixed or limited scale, such as 0 to 10, having the advantage of equidistant points between response categories (46). Examples: Pain track, computerized system with a 7-step-graded, fixed-point, non-verbal scale (76).

Table II. *Laboratory studies in the evaluation of pruritus*

Initial tests:
- Erythrocyte sedimentation rate (ESR)
- Complete blood cell count (CBC) with differential leucocyte count
- Blood urea nitrogen, creatinine
- Liver transaminases, alkaline phosphatase, bilirubin
- Fasting glucose, HbA1C
- Thyroid function test (thyroid stimulating hormone (TSH) and thyroxine levels)
- Parathyroid function (calcium and phosphorus levels)
- Serum iron, ferritin
- Chest X-ray
- Stool for ova, parasites and occult blood

Then:
- Serum protein electrophoresis
- Serum immunoelectrophoresis
- Antinuclear antibody (ANA)
- Extranuclear antibody (ENA)
- HIV
- Allergy diagnostic approach: total IgE, histamine, serotonin
- Prick tests of major atopy antigens and additives, patch tests
- Urine for sediment, 5-hydroxyindolacetic acid (5 HIAA) and mast cell metabolites
- Additional radiographic and sonographic studies

Table III. *Histological findings and probable diagnoses in clinically normal pruritic skin*

Histological finding	Probable diagnoses
Eosinophils in oedematous dermis or without epidermal changes	Allergic hypersensitivity, with e.g. drug Arthropod reaction
Eosinophils along the dermal-epidermal junction	Urticarial stage of pemphigoid with or without spongiosis
Neutrophilic microabscesses in the dermal papillae	Dermatitis herpetiformis
Increased number of mast cells around blood vessels in the absence of other inflammatory cells (except eosinophils)	Mastocytosis
Oedema in the dermis with a few or rare eosinophils	Urticaria
Fiberglass fragments	Fiberglass dermatitis
Deposition granula	Deposition disease

Continuous scales: The visual analogue scale (VAS) is the most common example in pruritus research (77). A continuous scale is a line of defined length (in most studies 100 mm) with descriptive anchors at the extremes, e.g. "no pruritus" and "pruritus as bad as it could be". Subjects can describe the itch sensation precisely without limitation to a few discrete categories, thereby providing continuous data for analysis. This may represent the most sensitive approach to measuring pruritus intensity (76).

Scratch-behaviour measurement limits the symptom because pruritic diseases such as urticaria and mastocytosis rarely cause scratching (and instead rubbing or pressing). Clinicians evaluate scratch behaviour by registration of lichenification and excoriation that vary widely. There are several measurement characteristics: *(i) self-report of scratching behaviour* – patients can be provided with hand-activated counters to record their scratching (78), but recording of nocturnal scratching is not possible; *(ii) nocturnal bed movements* – body movement at night is measured by a vibration transducer on one of the legs of the bed. Limb activity is measured with movement-sensitive meters (79). Nocturnal scratching can also be measured using an infrared video camera providing interesting data, but this is not suitable for routine monitoring in clinical use (80); *(iii) limb activity meters* – patients responding to nocturnal pruritus tend to move their arms more than their legs, and careful analysis of this ratio provides insight into scratching behaviour; *(iv) forearm activity meters* – rhythmic muscle potentials can be recorded simultaneously with an electroencephalogram recording sleep activity; *(v) direct observation* – expensive, time-intensive and with the potential for scratching behaviour underneath the covers to go unnoticed.

Questionnaires

- *The Worcester Itch Index* was developed at the University of Massachusetts at Worcester (1).
- A *questionnaire for uraemic patients and other forms of pruritus* is based on the short form of the McGill Pain Questionnaire (81–84). In 145 patients suffering from uraemic pruritus (81), dialysis was found not to influence uraemic pruritus that tends to be prolonged, frequently intense and a major source of distress to the patient. A modified form of this questionnaire has been used for evaluating patients with psoriasis (82), chronic idiopathic urticaria (83) and atopic dermatitis (84) and found to be reliable and reproducible (81–84).
- *The Eppendorf Itch Questionnaire* was developed in cooperation between dermatology and neurophysiology as a modified McGill Pain Questionnaire (85). It is informative in describing pruritus but does not evaluate other important characteristics, such as the effect of for example daily habits, physical activities on pru-

ritus or antipruritics. Evaluation of 108 patients suffering from AD in three different dermatology centres revealed that pruritus and objective AD severity (SCORAD index) are not directly proportional, but nevertheless related to each other to some degree (86).

PRURITUS IN DERMATOLOGIC DISEASE

This section focuses on the sensation of pruritus in dermatoses in which pruritus is a characteristic feature and an important problem. A more comprehensive discussion of the dermatological diseases mentioned can be found in dermatology textbooks.

Infestation

Scabies: Pruritus in scabies can be localized and has a burning character due to local reaction to the presence or activity of the mite. It can also be generalized, starting 4 to 6 weeks after infestation of the mite, and reflecting a generalized reaction to components of the mites, eggs or scybala (1). In scabies, pruritus typically intensifies at night. Family members and friends of the patient who is experiencing pruritic symptoms may also need to be assessed for infestation.

Pediculosis (lice): It is rare to make the diagnosis of pediculosis without pruritus as a symptom. Pruritus of body regions dense with hair follicles may be a clue to this diagnosis, though the infestation can be generalized (1).

Others: *Insect bite reactions*, e.g. mosquito bites; bedbugs (*Cimex lectularius* = common bedbug, *cimex tropica* = tropical bedbug); fleas (*ctenocephalides felis* = cat flea, *ctenocephalides canis* = dog flea); schistosomial cercarial dermatitis ("swimmers' itch").

Inflammation

Atopic dermatitis: Pruritus is such an important aspect of AD that "the diagnosis of active AD cannot be made if there is no history of pruritus" (87). The sensation is not constant, but comes in "attacks" which can be severe and disruptive to quality of life (88). A number of both immunologic and non-immunologic stimuli may provoke pruritus in patients with AD, e.g. heat and perspiration, wool, emotional stress, certain foods, alcohol, contact with air (*atmoknesis*) and common colds (36, 89).

Despite intensive research, the mediators of itch in AD have not been clearly determined. Because of controversial findings in plasma histamine levels there is evidence both for and against histamine involvement in the pathogenesis of AD (90). The minimal or moderate help of antihistamines indicates that histamine cannot be the only pruritogen and is most likely not the predominant media-

tor responsible for the pruritic sensation, though it has to be borne in mind that urticarial symptoms can form part of AD (88).

Treatment with antihistamines is generally thought to benefit the patient only by a central mechanism concerning sedation (91). Antihistamines are more likely to be effective in Th2-driven (early, more acute) AD than in Th1-driven (late, more chronic) AD (90). According to an evidence-based review, there is little objective evidence to demonstrate relief of pruritus in AD (92). It has been shown that the quality of sensation evoked by acetylcholine and vasoactive intestinal polypeptide depends on the inflammatory or non-inflammatory state of atopic skin and differs from healthy skin (28). Acetylcholine may induce a burning sensation in healthy persons, pruritus in patients with acute AD and a mixture of pain and pruritus in patients with eczema-free patients (28). These data provide evidence that pruritus can be elicited in AD by a cholinergic, histamine-independent mechanism.

Opioids constitute another class of neuropeptides that can cause pruritus. Naloxone, an opioid antagonist, has shown some antipruritic potency in skin diseases in an uncontrolled study, but only very poor efficacy in AD (93). Other studies suggest a possible role of SP and CGRP, both of which have been detected in AD (50). SDZ ASM 981, a selective inhibitor of the production of pro-inflammatory cytokines from T cells and mast cells in vitro including interleukin-2, -4, -10 and interferon-γ has shown antipruritic potency (94). Other therapies that specifically inhibit calcineurin-related activation of T lymphocytes have also proved to be sufficient antipruritics (oral cyclosporine, topical tacrolimus). An ongoing study shows that there is a significant relationship between the reduction of EASI scores in AD and the reduction of pruritus with tacrolimus treatment (pers. comm., Alan B. Fleischer Jr.). As the inflamed skin in AD contains several proinflammatory cytokines, they may play a role in pruritus. Thus far, only interleukin-2 has shown moderate pruritic potential, indicating that other unknown mediators might be involved (71). In summary, it can be assumed that mediators synthesized and released by cell types such as nerve cells, keratinocytes or inflammatory cells are responsible for the pruritus in AD (95, 96). The interactive network of nerve fibres expressing high-affinity receptors of various immune and inflammatory mediators may explain why different trigger factors are capable of modulating pruritus perception in AD (96).

Lichen simplex chronicus (neurodermitis circumscripta): Severe, paroxysmal pruritus leads to repeated rubbing and scratching in one spot, resulting in a thick, lichenoid plaque. Consequently, the main goal of therapy is the cessation of pruritus, which may be achieved by topical corticosteroids, doxepin cream, topical immunomodulators, capsai-

cin cream, topical aspirin or a creative combination of these (also see "Pruritus Therapy", p. 22).

Urticaria: This entity may be intensely pruritic, stinging or prickling, particularly in the acute phase with early lesions and small superficial wheals (1). Histamine plays a primary role in the pruritus of urticaria and H1 blocking agents decrease or eliminate this sensation in almost every case (46). Newer, multifunctional antihistamines such as levocetirizine or desloratadine may have additional non-histaminic therapeutic effects, including inhibition of leukocyte migration and mast cell stabilization (46). In summary, urticaria is the only known histamine-mediated pruritic disease in which antihistamines represent a causal therapy.

Irritant and allergic contact dermatitis: Feelings of pruritus and stinging may occur in the absence of visible skin lesions, especially in the early phase of irritant or allergic contact dermatitis.

Lichen planus can occasionally present as asymptomatic, but in most cases pruritus is severe, yet excoriations are rarely seen (46).

Mastocytosis: These are systemic and cutaneous forms of mastocytosis in which pruritus is often prominent and the most common symptom (46). In all forms, a symptomatic and pruritic dermographism combined with the Darier's sign (wheal, erythema, itching after a brisk stroke to a lesion) has been known to occur. Cases with no clinically obvious skin lesions but only generalized pruritus or dermographism have been reported (1).

Bullous diseases: In bullous pemphigoid, pruritus may either be absent or intense and generalized (97). It can precede the development of skin lesions by periods greater than 3 months (98). Pruritus in dermatitis herpetiformis is known for its burning, stinging or "firey" character, especially on the scalp (1). Scratching can be so intense that in many cases blisters are uncommonly observed compared to secondary excoriations and crusting. Pruritus in linear IgA bullous dermatosis is less severe but noted to occur.

Psoriasis: Although psoriasis is not typically regarded as an itching disease, studies have shown that up to 84% of patients suffer from generalized pruritus (82, 99). Seventy-seven percent report the symptoms on a daily basis – mainly in the evening and at night (82). In hospitalized patients, 92% report pruritus at some time (1). Higher prevalence and intensity of itch in some psoriatic populations may be related to high ambient temperatures in a tropical climate (82). Exacerbation of itch intensity has been noted as caused by heat, skin dryness, sweating or stress (82, 99). The most commonly involved areas are the back, legs, arms, buttocks and abdomen, but in hospitalized patients the scalp is the most frequently affected site (1). The pru-

ritus is mostly described as having tickling, crawling and burning components (82). Antihistamines do not relieve the pruritus in these patients (1, 82).

Parapsoriasis: Whereas small plaque parapsoriasis is typically not pruritic, increasing pruritus in large plaque parapsoriasis should be suspected as a progression to cutaneous T-cell lymphoma (CTCL) (1, 46).

Pityriasis rubra pilaris: Moderate to severe pruritus has been described in some cases (100), especially in early stages of the disease (101).

Prurigo nodularis is characterized by chronic and severe scratching, which is usually (but not always) the consequence of a pruritic sensation (1). Increased immunoreactivity to SP and CGRP can be seen (102). It is not known whether this is causal or secondary as a consequence of chronic scratching. As these neuropeptides are histamine-liberating agents, they may be responsible for the severe pruritus (102). An increase in the number of mast cells and eosinophilic degranulation is present (46, 102). Atopic diathesis is a contributing factor characterized by young age of onset and cutaneous hypersensitivity to various environmental allergens (46, 102). Exclusion of the systemic causes of pruritus and resolution of the underlying disorder are components to therapy. Topical therapy comprises emollients, potent or super-potent corticosteroids reinforced by occlusion to enhance penetration and to prevent mechanical manipulation. Capsaicin (0.025% to 0.3%) four to six times daily (103) and calcipotriol ointment twice a day have been reported as successful (104). Intralesional corticosteroids are limited in application owing to the high number of lesions. Combining with cryotherapy may be an alternative, but depigmentation has been reported (46).

Thalidomide (50 to 200 mg/day) may be the most effective treatment (46, 102). A minimum of 3 months of therapy is required to obtain long-term benefit. Thalidomide can also be used in AIDS patients without having immuno-compromising effects. Cyclosporine (3–4.5 mg/kg per day), systemic corticosteroids, etretinate, benoxaprofen (non-steroidal anti-inflammatory agent), phototherapy (UVA, UVB) and photochemotherapy (PUVA) have also reported efficacy (46, 102).

Polymorphic light eruption: This typically occurs in spring and summer and presents with pruritus. Polymorphic light eruption sine-eruption is intense pruritus on sun-exposed skin without visible changes. The condition may be difficult to distinguish from brachioradial pruritus.

Aquagenic pruritus can be either a common and trivial condition or a severe symptomatic disorder. One survey study shows a population prevalence of 45%, and of those affected 33% report a positive family history (105). The following criteria have been proposed for the diagnosis of aquagenic pruritus: *(i)* Severe pruritus occurring after wa-

ter contact irrespective of water temperature. *(ii)* Pruritus developing within minutes of water contact without visible skin changes. This excludes all causes of urticaria as well as symptomatic dermatographism. *(iii)* Chronic skin diseases, drug-related pruritus and internal disorders (including polycythaemia rubra vera (PRV) and other myeloproliferative diseases) have been excluded.

In aquagenic pruritus, prickling, tingling, burning or stinging sensations occur up to 30 min following contact with water and last for as long as 2 h (1) irrespective of water temperature or salinity. Typically, symptoms begin on the lower extremities and generalize, with sparing of the head, palms, soles and mucosae (106). Many aetiologies for aquagenic pruritus have been reported (Table IV). The pathologic mechanism is unknown, although elevated dermal and epidermal levels of acetylcholine, histamine, 5-hydroxytryptamine and prostaglandin E_2 have been reported (1).

Traditional therapies utilize alkalinization of bathwater to a pH of 8 with baking soda, and systemic treatments include oral cyproheptidine, cimetidine or cholestyramine. These have shown minimal effectiveness (106). In the setting of PRV, aspirin may give partial relief, but the risk of gastrointestinal haemorrhage is increased (1). More recent reports show efficacy of suberythemal UVB (290 to 320 nm) irradiation or oral psoralen photochemotherapy (PUVA) (106). Capsaicin cream (0.025%, 0.5% or 1.0%) applied 3 times daily over a minimum of 4 weeks minimizes symptoms, but may not be practical for long-term therapy (107).

Eosinophilic pustular folliculitis (Ofuji's disease): This rare disorder was originally found in Japan and is seen most often in immunocompromised individuals with AIDS,

Table IV. *Differential diagnosis of pruritus or prickling sensations provoked by water contact*

Skin pathology evident
Polycythaemia rubra vera
Hodgkin's disease
Mastocytosis
Hypereosinophilic syndrome
Myelodysplastic syndrome
Essential thrombocythaemia
Idiopathic haemochromatosis
Heat or cold pruritus
Alcohol-induced itching on hot shower in sarcoidosis
Aquagenic pruritus (idiopathic)
Skin pathology typically absent
Cold urticaria
Cholinergic urticaria (secondary to hot water exposure)
Aquagenic urticaria
Aquagenic pruritus of the elderly (xerosis; may be subtle)
Eczematous dermatitis (exacerbation by water contact)

myeloproliferative diseases and visceral carcinomas (108). Itching may be so severe that primary pustules cannot be identified.

Prurigo pigmentosa: This is a rare dermatitis of unknown origin. It was first described in 1971 (109) and mainly affects Japanese women in spring and summer. Only a few cases affecting other ethnic backgrounds have been reported. It is characterized by the sudden onset of intensely pruritic and reddish papules that leave reticular pigmentation when healed (110). The chest, upper back, clavicular region and neck are the most affected body areas. As the histological features are non-specific, the diagnosis is based on the striking clinical appearance. Minocycline 100–200 mg daily is the therapy of choice. Dapsone, sulfamethoxazole and macrolide antibiotics (clarithromycin 400 mg/day, roxythromycin 300 mg/day) are also effective (110) in decreasing pruritus and skin symptoms.

Infections

Fungal infections: Inflammatory tinea and other superficial fungi may be intensely pruritic (46). Candida is the most important infectious agent to consider in perineal pruritus or burning sensations (1). "Barn itch" in rural workers is due to Trichophyton verrucosum infection from animals (111). Pityrosporum folliculitis has been increasing in prevalence (46).

Bacterial infections: Folliculitis caused by Gram-positive or Gram-negative bacteria, impetigo and bacterial intertrigo may present with pruritus. One-third of patients with secondary syphilis complain of this symptom. The primary lesion of cat scratch disease may resemble an insect bite and is generally not pruritic. However, a case has been reported in which the patient's main symptom was a pruritic rash (112).

Viral infections: Varicella is characterized by pruritus that can severely increase when the immune system is impaired (e.g. HIV, malignancy). Herpes simplex infections often have a pruritic and stinging component: first-episode genital herpes patients have local pain and pruritus in 98% of cases (46). In acute Herpes zoster and post-herpetic neuralgia, burning or lancinating pain predominate, but pruritus may be present as well. A wide variety of viral exanthems can present as pruritic rashes, particularly in childhood (46).

Neoplastic

Cutaneous T-cell lymphoma (CTCL): Intensive pruritus is experienced by 70–80% of patients (1). Persistent generalized pruritus as the only cutaneous manifestation of CTCL without any skin lesions has been described recently (3). Moreover, one study detected that deaths due to CTCL

were twice as common among those with pruritus (113), which should lead to pruritus being added as a B-symptom in CTCL.

Hereditary

Darier's disease: Patients may experience severe pruritus and discomfort that can be aggravated by heat and UV exposure. The lesions in ILVEN (inflammatory linear verrucous epidermal nevus) are characteristically pruritic.

Miscellaneous

Xerosis is most common in elderly people (see below), but generalized forms can also be caused by drugs such as cimetidine and retinoids. HIV infection seems to predispose toward xerosis and asteatotic dermatitis (46). Excessive bathing in hot water, soaps, detergents and use of irritant topicals containing alcohol or allergens can induce xerosis and lead to eczema craquelé accompanied by pruritus.

Pruritus in aged skin: Of the aetiologies for generalized pruritus in the elderly, xerosis or dry skin may be the most common (114). Owing to atrophy of the integument and a decrease in skin vascular supply with age, lipid composition changes and moisture retention is compromised, leading to a scaling of the epidermis usually with no erythema or eruption. Chronic diseases such as hepatic or renal failure, diabetes and thyroid disorders are common in the elderly population and may be aetiologies of generalized pruritis (115). Polypharmacy leads to the possibility of drug-induced pruritus. Institutionalized care, e.g. nursing homes, predisposes the patient to infections aetiologies of pruritus such as lice, scabies and other mites. Psychogenic pruritus and elderly pruritus are to be considered when other causes have been excluded. It is characterized by an intensity that parallels the emotional state and is often exaggerated (115). The patient's sleep pattern is usually uninterrupted and may require sedative antipruritics for treatment because topicals are rarely effective. A depression screen may be performed, because this psychiatric illness has been associated with generalized pruritus. Psychotic patients occasionally have generalized pruritus for which no cause is apparent and may have delusions of parasitosis.

Elderly pruritus has been speculated to occur secondary to processes associated with ageing, such as atherosclerotic disease, cerebrovascular accidents and degenerative changes in peripheral nerve endings. Neurologically active compounds such as amitriptyline or carbamazepine, as well as topical moisturizers and emollients, have been reported as effective in post-stroke pruritus (116). Ideal therapy would be reversal of the disease state, but this is not available at this time.

Treatment in aged skin should include avoidance of frequent hot or cold bathing practices and instead bathing in lukewarm water using moisturizing soaps. Frequency may be restricted to once or twice weekly with intermittent sponge bathing of odorous regions such as axillae and the groin/buttocks. The body should be blotted dry, because rubbing or wiping will exfoliate more of the thinned epidermis. Moisturizing creams, lotions or ointments are applied soon after and repeatedly each day.

Pruritus ani is defined as pruritus localized to the anus and perianal skin. It occurs in 1–5% of the general population and males are more commonly affected than females by a ratio of 4:1 (117). Onset is insidious and symptoms may be present for 5–7 weeks up to many years before patients seek medical attention.

Primary (idiopathic) pruritus ani describes pruritus in the absence of any apparent anorectal or colonic aetiology. The incidence ranges from 25% to 95% of reported cases and many causes have been hypothesized (117). More common are dietary factors such as excessive coffee intake, poor personal hygiene and/or anal seepage, psychogenic disorders and radiation. Secondary pruritus ani describes perianal pruritus attributable to an identifiable aetiology. These include haemorrhoids, anal fissures or fistulas, psoriasis or lichen sclerosis and other dermatoses, sexually transmitted diseases and neoplastic pathology.

Physical examination findings vary from normal appearing skin through mild erythematous change of the perianal area to severe irritation including erythema, skin ulcerations, lichenification and exsudates. Histopathologic diagnosis typically shows non-specific chronic dermatitis, but may be helpful in identifying a specific dermatologic or neoplastic disease (118).

Patch-testing should be considered in patients who do not respond to initial treatment, since a recent study demonstrated that 34 of 40 patients presenting with pruritus ani had an underlying dermatosis that accounted for their symptoms, including allergic contact dermatitis (119). Rectosigmoidoscopy and/or colonoscopy may be necessary, particularly in cases of pruritus ani refractory to conventional treatment. In a case series of 109 patients with pruritus ani as their presenting complaint, 83 (75%) had colon and anorectal pathologies ranging from haemorrhoids to cancer (26 patients had the latter diagnosis) (117). If patients are on chronic antibiotic therapy and have liquid stools, pH testing may be performed. A pH of 8–10 may be associated with a deficiency of lactobacillus requiring replacement therapy (120). Psychiatric screening is of importance as anxiety and depression have been quoted as aggravating factors (119).

Mild primary pruritus ani may respond to sit baths, cool compresses and meticulous hygiene. Patients can be instructed on how to perform a "rectal gargle" with warm water and a bulb syringe after defecation. The area is then blotted dry, with avoidance of rubbing and stringent soaps. A mild corticosteroid cream (hydrocortisone, fluocinolone, desonide) has been shown to be effective in controlling symptoms. However, with long-standing disease and lichenification, patients may need prolonged treatment, raising the risk of atrophogenesis. Topical immunomodulators such as tacrolimus may be needed for ongoing use. Secondary pruritus ani improves with treatment of the underlying disorder (e.g. extirpation of malignancy, anti-helminthic therapy, haemorroidectomy).

Pruritus vulvae and scroti may be as common, incapacitating and emotionally disturbing as anal pruritus (1). Originally thought to be psychogenic illnesses, reports indicate that these are psychogenic in only 1.3–7% of cases (121). Pruritus is worse at night and lichenification may develop through repeated trauma. The work-up, differential diagnosis and treatment options (including the use of tacrolimus) are similar to pruritus ani. Additionally, clobetasol ointment applied twice daily for 2 weeks to 2 months often produces rapid response in vulvar lichen sclerosus and in lichen simplex chronicus of the scrotum and the vulva. Topical testosterone propionate has also been reported as effective, but carries a significant risk of androgenizing effects (46).

Pruritic scalp: Any pruritic skin disorder such as psoriasis may present with symptoms localized to the scalp, and all efforts to identify such a problem should be made. However, pruritus of the scalp can occur in the absence of any objective changes. This is seen commonly in middle-aged individuals and is frequently related to periods of stress and fatigue. Despite the high prevalence of pruritus, the scalp is less sensitive to histamine-induced experimental pruritus. This provides evidence that other local mediators, e.g. proteases or central mechanisms, must be assumed (20).

Various treatments, such as emollients, antipsoriatic and/or corticosteroid topicals, have been employed, albeit with low rates of success (1).

Amyloidosis, mucinosis: Amyloidosis in the form of familial primary cutaneous amyloidosis has been reported to be associated with severe pruritus beginning in childhood. Lichen amyloidosis, macular amyloidosis and mucinosis-predominant diseases such as lichen myxedematosis and follicular mucinosis may be intensely pruritic. It has to be considered that repeated friction or trauma to the skin may lead to the deposition of significant amounts of degenerated keratin and that is why cases of macular amyloidosus are in fact due to, or identical with, notalgia paresthetica (122).

Fibreglass dermatitis: This can be so severe and difficult to diagnose that in an extreme case incarceration for lewd and indecent scratching occurred (123). Fibreglass expo-

sure is common in industrial and construction occupations and may provoke severe pruritus with or without visible skin lesions. Involvement of the hands and other exposed parts of the body, such as the upper extremities, face and trunk, is typical. Clinically, fibreglass dermatitis may resemble scabies, hand dermatitis, folliculitis or urticaria (46).

Pruritus in scars associated with normal healing is common and resolves quickly (1). Occasionally, pruritus and discomfort may be prolonged and hint at abnormal healing, such as hypertrophic and keloidal scarring. The pruritic sensation in scars is probably a consequence of physical, as well as chemical stimuli and nerve regeneration. Physical stimuli include mechanical and electrical excitation, heat, negative pressure or suction. In addition, chemical mediators such as histamine, vasoactive peptides including kinins and prostaglandins of the E-series (PGE) are involved. The role of histamine in the early and inflammatory phase of wound healing is well documented. The increased histamine content in keloids and hypertrophic scars appears to parallel the rate of collagen synthesis (1). Although both kinins and PGE promote vasodilatation, the latter mediates the effect of histamine via cyclic AMP and direct histamine release. Increased levels of chemical mediators such as histamine, bradykinin and prostaglandin present in early wounds and abnormal scars may account for a "chemogenic" pruritus that is separate from the sensation elicited by mechanical stimulation (1). Nerve regeneration occurs in all healing wounds and a disproportionate number of thinly myelinated and unmyelinated C-fibres present in immature or abnormal scars contribute to the increased perception of pruritus.

Scar remodelling can last between 6 months and 2 years. It is likely that all described factors, including direct mechanical stimulation of nerve endings during scar remodelling, account for the perception of pruritus in elevated, abnormal or immature scars (1).

Therapy is difficult, and includes emollients, anti-inflammatory agents such as topical and intralesional corticosteroids and interferons, topical retinoic acid, silicone gel sheets or cream. Oral antihistamines do not provide any great benefit. The successful relief of pain and pruritus of giant keloids using pentoxifylline (400 mg) twice or three times daily has been reported (124).

Postburn pruritus: Approximately 87% of patients with burns complain of severe pruritus, particularly with leg or arm wounds (125). Histamine release during the inflammatory stage of the healing process is a by-product of collagen production (126), supporting the idea that post-burn pruritus may be a variant of scar pruritus. Morphine is the analgesic of choice in the treatment of burns and may contribute to post-burn itching (127).

Survivors often face psychological and physical consequences resulting from financial costs and stress linked to an increase in pruritic sensations (128). Therapy comprises topical emollients and antihistamines, but these rarely provide adequate relief (128). Newer reports favour a topical anaesthetic (lidocaine/prilocaine, EMLA), a combination of shower and bath oil with colloidal oatmeal 5% and massage therapy (128, 129).

PRURITUS IN SYSTEMIC DISEASE

Uraemic or renal pruritus

Renal pruritus is a paroxysmal pruritus occurring in patients with chronic (not acute) renal failure. Unfortunately, the term "uraemic pruritus" is often used synonymously. "Uraemic pruritus" implies that the symptom is secondary to raised serum urea levels, which is untrue. The incidence of pruritus in end-stage renal disease undergoing haemodialysis used to vary from 60% to 80% (76, 130, 131), but nowadays it varies from only 15% to 20% (74). The reason for this decrease might be sought in both a higher biocompatibility of dialysis and in a tighter control of dialysis adequacy (74). For this group of patients the term "haemodialysis-related pruritus" may be more appropriate. Pruritus in paediatric patients on dialysis occurs in 9.1% (74).

The occurrence of renal pruritus is unrelated to sex, age, race, duration of dialysis or aetiology of the renal failure. Patients on continuous ambulatory peritoneal dialysis are less affected than patients on haemodialysis (1). Pruritus peaks at night after 2 days without dialysis; it is relatively high during treatment and lowest during the day following dialysis (76, 81). Renal pruritus has been shown to be an independent marker of mortality for patients on haemodialysis. The intensity and distribution of pruritus vary from sporadic discomfort to complete restlessness. About 25–50% of patients suffer from generalized pruritus, whereas others are affected mainly on the back, the face and the shunt arm (74, 130).

The aetiology is still poorly understood. The role of mast cells is controversial: studies have detected mainly degranulated, diffusely spread, and more numerous mast cells (132, 133) in patients with pruritus than in patients without pruritus (132). Proliferation of mast cells in various organs (spleen, bone-marrow, bowel wall) and skin (134–136) has been reported, but no significant difference has been found between patients in non-dialysis end-stage renal failure and controls (135). No relationship has been found between the number of mast cells in end-stage renal failure with or without pruritus (135). Other studies have been unable to confirm these findings (137–139).

Increased plasma histamine levels have been detected in uraemic patients (132, 140–145). Whereas studies have shown higher plasma histamine levels in haemodialysis patients with pruritus than in those without it (141, 142,

144, 145), no relationship has been found between plasma histamine level and severity of pruritus (140). Others have not detected elevated plasma histamine levels (139, 146, 147). This finding is in accordance with the common experience that antihistamine therapy often fails to provide sufficient relief.

Another hypothesis describes a possible role of accumulation of poorly dialysed compounds that cross dialysis membranes more slowly (1).

Parathyroid gland activity is commonly increased in chronic renal failure and dramatic relief of pruritus after subtotal parathyroidectomy has been reported (1). Parathyroid hormone (PTH) has been shown to be significantly higher in dialysis patients with pruritus than in those without, but there was no correlation between the degree of symptoms and the PTH level (76, 148). Immunohistochemical studies have failed to demonstrate the presence of PTH in the skin or produce pruritus when intradermally injected (76). Additionally, pruritus is not always present in uraemic patients with hyperparathyroidism (76). In summary, the role of circulating PTH in renal pruritus remains controversial.

Xerosis is a common finding in uraemic patients, but the presence of pruritus does not correlate with xerosis, stratum corneum hydration or sweat secretion (149, 150).

Whole blood serotonin levels are elevated in haemodialysis patients (151), while free plasma serotonin levels are not (147). Serotonin's role remains unclear, especially since controlled studies have failed to show an antipruritic effect of ondansetron, a 5-HT3 receptor antagonist in haemodialysis patients (152, 153).

Peripheral neuropathy affects 65% of patients who are on dialysis and raises the possibility that pruritus may be a manifestation of neuropathy (1). Specialized receptors for pruritus have also been proposed in the chronic dialysis patient, but do not explain the abruptness of the response to transplantation (1).

Opioids and alterations of the immune system are currently the most frequently discussed pathophysiological concepts. Opioids potentially play a role, because they accumulate in renal failure. However, this is unrelated to the duration of disease and unaltered by haemodialysis (1). One study states that renal pruritus is not related to β-endorphin serum levels in haemodialysis patients (65). Finally, immunologic mechanisms have gained more attention, emphasizing the importance of Th1 and Th2 lymphocyte interaction (74, 154). Various cytokines are released during haemodialysis and may lead to the release of inflammatory and potentially pruritogenic substances (155). CD1+ cells can contribute to the development of renal pruritus, as these cells have been found in greater number in pruritic patients (155). Patients with renal pruritus have been found to have a more pronounced Th1 differentiation compared to patients without pruritus (74). Be-

cause of the improved biocompatibility and dialysis efficacy following the use of high flux dialysis membranes, complement and leukocytes are less activated than conventional materials are (74). A recent publication hypothesizes an immunologic impairment conveyed by uraemia, since a 7-day topical application of tacrolimus in 3 patients led to dramatic relief of pruritus (156). This observation may be interesting, but it has to be interpreted with caution as the therapeutic effect could also have been due to moisturizing properties. Besides, there is no obvious explanation as to how the immunomodulatory activity of tacrolimus could effect renal pruritus. A brief overview of published therapeutical options is given in Table V.

Antihistamine use has shown only marginal efficacy in renal pruritus (1). Oral activated charcoal has produced good results in controlled studies, but cholestyramine has been used with varying success (1). Other reports state success with ketotifen, i.v. heparine, lidocaine and erythropoietin (1). Ondansetron has been reported as successful in continuous ambulatory peritoneal dialysis and HD patients (157), but this is not verified in the latest studies in HD patients (152, 153). While thalidomide (100 mg) therapy relieved pruritus in a significant number of patients in one controlled study (158), controlled studies of naltrexone 50 mg/day remain controversial (159, 160).

Phototherapy with UVB, but not UVA, has been shown to be beneficial in double-blinded trials (1, 46). Topical capsaicin application has demonstrated efficacy in renal pruritus in haemodialysis patients (161, 162). However, effective dialysis and renal transplantation are the most effective treatments because pruritus ceases quickly after these procedures (1, 163).

Hepatic or cholestatic pruritus

Almost all liver diseases present with pruritus. The most commonly associated entities are primary biliary cirrhosis, primary sclerosing cholangitis, obstructive choledocho-

Table V. *Therapeutic options in renal pruritus*

Effect confirmed in controlled trials:
-Activated charcoal 6 g/day (1)
-UVB phototherapy (1)
-Thalidomide 100 mg/day (158)
-Topical capsaicin 3–5 times daily (161, 162)

Equivocal effect in controlled studies:
-Naltrexone 50 mg/day (159, 160)
-Ondansetron 8 mg orally or i.v. (152, 153, 157)

Effect confirmed in case series or case reports:
-Cholestyramine (1)
-Erythropoietin 36 U/kg body weight three times a week (145)
-Lidocaine 200 mg i.v./day (1)
-Ketotifen 1–2 mg/day (141)

lithiasis, carcinoma of the bile duct, cholestasis (also see drug-induced pruritus), chronic hepatitis C and viral hepatitis (1). Less commonly associated liver diseases are alcoholic cirrhosis, haemochromatosis, Wilson's disease, chronic hepatitis B and autoimmune chronic active hepatitis. Pruritus as a presenting symptom of primary biliary cirrhosis is reported by 25–70% of patients and is experienced by at least 80% (66). Pruritus is noted in 15% of hepatitis C-positive patients (164, 165). According to a recent case-control study, the hepatitis C virus rate in patients with chronic pruritus is equivalent to the rate in the general population. The authors conclude that routine testing for hepatitis C virus is not justified in the absence of risk factors (166). It is emphasized that drug-induced cholestatic jaundice presenting with pruritus can develop within a short time course and affect patients with no history of liver disease (167). Pruritus has also been mentioned as a presenting feature of the arteriohepatic syndrome in children (168).

Cholestatic pruritus tends to be generalized, migratory, not associated with any specific skin lesion and not relieved with scratching (169). It is typically worse on the hands and feet, body regions constricted by clothing, and is most pronounced at night. It can be an early symptom in chronic cholestasis, developing years before any other manifestation of liver disease (1). This symptom may be overlooked even in patients with chronic liver disease unless a careful history is elucidated.

The aetiology of cholestasic pruritus is unknown. There are several major theories about mediators and mechanisms. For decades, bile acids have been postulated as playing a role. While on the one hand intracutaneous application has been reported to induce pruritus, on the other hand elevated serum concentrations of bile acids are not always associated with pruritus. Additionally, in patients with severe cholestasis the development of hepatocellular failure tends to result in the spontaneous cessation of pruritus (66).

Another hypothesis proposes that increased opioidergic neurotransmission or neuromodulation (tone) in the CNS contributes to pruritus of cholestasis (66). Other observations indicate that opiate agonists induce opioid receptor-mediated scratching activity of central origin. Furthermore, cholestasis-related changes in the opioid system may lead to changes in other neurotransmitter systems, such as altered serotoninergic neurotransmission leading to elevated metenkephalin levels (66).

The treatment of cholestatic pruritus depends on the underlying cause and includes gallstone removal, drug withdrawal, interferon therapy for chronic hepatitis C, and, ultimately, liver transplantation in end-stage liver failure. A number of systemic antipruritic therapy modalities have been reported as successful (Table VI). There is little evidence to suggest that ursodesoxycholic acid is effective in reducing pruritus in primary biliary cirrhosis, with benefit

Table VI. *Treatment of hepatic or cholestatic pruritus*

Effect confirmed in controlled clinical trials:
- Cholestyramine 4–16 g/day p.o. (66)
- Ursodesoxycholic acid 13–15 mg/kg/day p.o., not in PBC (1, 170)
- Rifampicin 300–600 mg/day p.o. (233)
- Naltrexone 50 mg/day p.o. (173, 174)
- Naloxone 0.2 μg/kg body weight per minute i.v. (234)
- Nalmefene 2–120 mg/day p.o. (235)
- Thalidomide 100 mg/day p.o. (237)

Equivocal effect in controlled studies:
- Ondansetron 4 mg or 8 mg i.v. or 8 mg p.o. daily (226, 238, 239)

Effect confirmed in case series or case reports:
- Plasma perfusion (ion resin BR-350) (46)
- Propofol 10–15 mg i.v. (bolus), 1 mg/kg/h (infusion) (236)
- Phenobarbital 2–5 mg/kg body weight/day i.v. (240)
- Phototherapy: UVA, UVB (46)
- Stanozolol 5 mg/day p.o. (241)
- Bright light therapy (10000 lux) reflected toward the eyes up to 60 min twice/day (242)

PBC: Primary biliary cirrhosis

being reported in only 2 of 11 trials reviewed in a recent meta-analysis (170). Current reports take into consideration colesevalem, a new bile acid sequestrant that appears to be more potent than cholestyramine and does not induce constipation (171). Rifampicin is effective in controlling pruritus in primary biliary cirrhosis and is frequently used as second-line treatment (172). In a recent case report, significant impaired hepatic synthetic function due to rifampicin monotherapy was observed in patients with primary biliary cirrhosis (172). Given the potential of rifampicin to induce significant hepatotoxicity, and the advent of more effective second-line antipruritic agents such as the opiate antagonists, the use of rifampicin should be restricted to patients who have failed to respond to other agents (172). Oral naltrexone was effective in two controlled studies in pruritus of cholestasis (173, 174). As there is no compelling evidence that histamine is involved in the pathogenesis of pruritus, antihistamines do not show any therapeutical benefit except sedating properties promoting sleep.

Haematologic pruritus

Haematologic diseases, especially the malignant conditions, are associated with significant pruritus.

Iron deficiency: Causes of generalized or localized pruritus in association with iron deficiency, especially in the perianal or vulval region, and even in the absence of anaemia, have been described responding to iron treatment (175, 176). No controlled trials have been performed, and thus the relationship between iron replacement and pruri-

tus has to be questioned. It has to be considered that iron deficiency can be a sign of PRV, numerous other cancers, or other systemic diseases which themselves cause pruritus. A pathogenetic role for iron deficiency in PRV-associated pruritus has been suggested (177).

Polycythaemia rubra vera (PRV): 30–50% of patients suffer from pruritus; in the latest retrospective cohort 48% had a documented history of pruritus (177). The presence of pruritus at diagnosis was significantly associated with a lower mean corpuscular volume and a higher leucocyte count (177). Water-induced pruritus may precede the development of PRV by years (see also "Aquagenic pruritus"). This diagnosis must therefore be suspected in all patients with water-induced pruritus (46). Platelet aggregation has been suggested as a possible mechanism leading to serotonin release and other pruritogenic factors including histamine. Treatment comprises topical corticosteroids, systemic H_1- or H_2-antihistamines, UVB phototherapy, aspirin, intramuscular interferon-γ and selective serotonin re-uptake inhibitors such as paroxetine (46, 178).

Malignancy and pruritus

Whereas true cutaneous metastases of malignant tumours are non-pruritic, virtually any malignancy can induce pruritus as a paraneoplastic disorder. The true relationship between cancer and this symptom is unclear. No reliable epidemiologic study has demonstrated whether malignant diseases are increased in patients suffering from pruritus. Persistent, unexplained pruritus, or failure of generalized pruritus to respond to conventional therapy, should warrant evaluation for an underlying malignant disease (46). Pruritus can be seen in advanced malignant disease or it may be an early sign (179). The intensity and extent of pruritus do not correlate with the extent of tumour involvement (1). Suggested mechanisms include toxic products of necrotic tumour cells entering the systemic circulation, production of chemical mediators of pruritus by the tumour, allergic reactions to tumour-specific antigen, increased proteolytic activity and histamine involvement.

Gastrointestinal malignancies can cause pruritus of varying degree secondary to extrahepatobiliary obstructive disease. In this setting, pruritus tends to be generalized, with the palms and soles areas of particular involvement.

Pruritus of the nostrils has been associated with tumours of the brain, but has not been observed with other malignancies (1).

Hodgkin's disease has a pruritus prevalence of 10–30%. Intense pruritus may precede the diagnosis by many months (180). Severe persistent, generalized pruritus predicts a poor prognosis, and return of this symptom may portend tumour recurrence (181). It has been proposed that it be added to the list of B symptoms in this disease (1).

Non-Hodgkin's lymphoma: Pruritus is generally less frequent (2%). Another 10% of patients suffer from pruritus at some time during the course of the disease.

Fewer than 5% of patients with leukaemia experience pruritus. When it does occur, it is more commonly generalized and found in the chronic lymphocytic variant. Malignant infiltrates may produce localized pruritus (46).

Endocrine pruritus

Thyroid disease: Severe generalized pruritus may be the presenting symptom in hyperthyroidism. The cause is not known, but is most likely explained by the effect thyroid hormone has on the skin (1). Localized or generalized pruritus can be seen in hypothyroidism, but is not reported as a frequent complication. The skin in hypothyroidism is dry, and thus can lead to asteatotic eczema accompanied by pruritus.

Diabetes mellitus: Generalized pruritus as a presenting symptom of diabetes can occur, but is not significantly more common than in non-diabetic patients (182). Localized pruritus, especially in the genital and perianal areas, is significantly more common in diabetic women and significantly associated with poor diabetes control (182). In a certain number of cases this may be due to predisposition to candidiasis or dermatophyte infections. The mechanism of pruritus induction in diabetes is not known. Diabetic neuropathy is more characteristically associated with pain, burning or a prickling sensation, although pruritic sensations have also been described (1).

Premenstrual or perimenstrual pruritus: Premenstrual pruritus related to recurrent cholestasis induced by oral contraceptives or other hormonal treatment is well recognized (1). Generalized pruritus related to menses and sensitivity to intradermal estrogen has been described (183). Episodic pruritus is an occasional symptom in perimenopausal women and can be treated by hormone replacement therapy (46).

Carcinoid syndrome: This can lead to generalized pruritus with or without a rash (1).

Multiple endocrine neoplasia type 2a: Localized pruritus of the mid to upper back or scapular area has been reported in association with multiple endocirine neoplasia type 2a, but differential diagnosis may include lichen amyloidosis and notalgia paraesthetica (1). In one report, a family is described as having localized pruritus occurring symmetrically on the back or crossing the midline. In all affected family members, the pruritus had been present long before the clinical or biochemical diagnosis was made (184).

Cholinergic pruritus: This has been described as an increasingly severe pruritus triggered by physical exertion,

warm surroundings, anxiety and hot food. It may respond to treatment with danazol (1).

Pruritus in HIV infection and acquired immunodeficiency syndrome (AIDS)

Pruritus is an important cause of discomfort and morbidity in HIV patients (185) and is an occasional initial presentation in AIDS. As many as half of AIDS patients may never have specific causative or categoric diagnoses identified (46). However, these patients are prone to develop a number of pruritic dermatoses, such as pruritic papular eruption, seborrhoeic dermatitis, scabies, drug eruptions, acquired ichthyosis, staphylococcal skin infections or Kaposi sarcoma. As photosensitivity is especially increased in advanced disease, patients may develop photodermatitis, usually due to photosensitizing drugs (185). Lichenoid photoeruptions, which mainly affect Afro-American patients, are accompanied by severe pruritus, violaceous plaques of the hands, forearms, face and neck, especially in cases of severe immunosuppression (186). Prominent hyperpigmentation and hypopigmentation may follow (185).

Eosinophilic pustular folliculitis may have excoriations and prurigo nodules as the most common findings (46). Insect bites are markedly more inflammatory and pruritic in the HIV-infected population. Norwegian scabies tends to be more common in this group as well. Severe acquired ichthyosis, frequently located on the extremities, can also be generalized and may be accompanied by pruritus. Kaposi sarcoma lesions can also be pruritic.

Systemic causes (other than HIV itself) are relatively uncommon, but need to be recognized in renal failure as a result of HIV nephropathy, hepatic failure due to hepatitis B or C and systemic lymphoma (185).

Patients have augmented serum concentrations of IgE correlated with a faster decline in CD4 counts (1). Basophils show enhanced degranulation in vitro. Immunologic analyses of patients with intractable pruritus have shown that hyper-IgE and hypereosinophilia are associated with the worst prognosis, and alterations in the type 1/2 cytokine profile are prognostically unfavourable (187). A possible correlation between intractable pruritus and augmented HIV viral load has been observed. Finally, it is postulated that the presence of these symptoms should stimulate more in-depth analysis and, perhaps, a more aggressive therapeutic antiviral approach (187).

Severe pruritus unresponsive to symptomatic treatment is relatively common. Treatment is best directed at the underlying dermatoses if those can be identified. Topical corticosteroids should be used with caution, as these can worsen immunosuppression. Phototherapy with UVB light can be beneficial (188), but for the same reason should be applied in a moderate pattern. Theoretically, phototherapy can increase HIV replication but, so far, no change has been found in the plasma viral levels of patients (189). Antihistamines may be used symptomatically and those with anti-eosinophilic potential might be more effective (e.g. cetirizine). Others favour doxepin, a tricyclic antidepressant with antihistaminic potential, as being particularly helpful in idiopathic pruritus at an advanced stage of the disease. Pentoxifylline 400 mg t.i.d. has been shown to be an efficacious treatment of pruritus in HIV-infected patients with pruritic papular eruption (190). This treatment, and the antipruritic effect of indomethacin in HIV-related pruritus (191), has not yet been confirmed in controlled clinical trials. The most promising therapeutic option for pruritus and prurigo nodularis in patients with HIV and AIDS is currently thalidomide (50–300 mg/day), which is not an immunosuppressant (192, 193).

PRURITUS IN PREGNANCY

Herpes gestationis: This is a rare, IgG-mediated autoimmune disease with anti-basement membrane antibody deposition and complement fixation along the epidermal side of the lamina lucida. Recent estimates of incidence vary from 1 in 10,000 deliveries to 1 in 50,000 (1). Onset occurs typically in the second or third trimester, but may develop during the immediate postpartum period. Lesions progress from pruritic and urticarial papules or plaques to a generalized pemphigoid-like eruption. The face, mucous membranes and palms/soles are usually spared. The disease resolves spontaneously several weeks to months postpartum, but recurs with increased severity in subsequent pregnancies.

Systemic corticosteroids are the cornerstone of therapy (0.5 mg/kg/day of prednisone). Topical corticosteroids, oral antihistamines, dapsone, pyridoxine, methotrexate, cytoxan, cyclophosphamide and plasmapheresis have shown mixed results. Most of the chemotherapeutic agents are contraindicated prior to delivery.

Pruritic urticarial papules and plaques of pregnancy is the most common dermatosis unique to pregnancy (1 in 160 deliveries) (194). This is an idiopathic, intensely pruritic, urticarial or papular dermatosis that tends to occur during the latter part of the third trimester or immediate postpartum period. Onset is abrupt, often within striae distensae. It commonly spreads to the trunk and extremities while sparing the face. Vesiculation can be present, but differs from herpes gestationis in that progression to bullous disease and specific immunofluorescent deposition at the dermal-epidermal junction are non-existent (195). Liver transaminases, hormone levels and HLA typing are normal and the aetiology remains unknown. Treatment with medium to high potency topical corticosteroids and oral antihistamines has proved to be effective. Occa-

sionally, systemic corticosteroids may be required. Phototherapy with UVB light is another treatment option. Resolution is typically seen within 1 to 2 weeks postpartum.

Cholestasis of pregnancy is an estrogen-dependent alteration in liver function resulting in cholestasis. It is the second most common cause of gestational jaundice behind viral hepatitis (196). A positive family history of cholestasis of pregnancy is seen in 50% of affected women.

Features of the disease include generalized pruritus with or without jaundice, which tends to be worse at night particularly on the soles, palms and trunk – biochemical profiles consistent with cholestasis and recurrence during subsequent gestation (197). Skin findings other than jaundice are rare. Treatment is purely symptomatic. Cholestyramine, S-adenosylmethionine, activated charcoal, ursodesoxycholic acid, dexamethasone and UVB phototherapy have shown inconsistent results. Oral guar gum, a gel-forming dietary fibre, has shown promise by lowering serum bile acid levels and pruritus scores with potentially fewer adverse effects than cholestyramine (198). Jaundice resolves within 1 to 2 weeks and pruritus within 24 to 48 h postpartum.

DRUG-INDUCED PRURITUS

Any drug can cause an adverse reaction in the skin that can be associated with pruritus (1). Most commonly, pruritic reactions will be morbilliform and urticarial, but one could also consider an adverse drug reaction in generalized pruritus without skin lesions. Some medication effects (such as hepatotoxicity) may have a latency period. Table VII indicates the more frequent and well-recognized drugs and their pathomechanisms leading to pruritus. Systemic administration of agents can cause non-specific pruritus (199). Severe, generalized or localized (mostly anogenital) pruritus persisting up to several months has been observed in 15–42% of patients who have received hydroxyethyl starch (HES) infusion therapy (200). This should be strongly considered in post-ICU pruritus. Its pathophysiology is not completely understood. Recent animal studies detected HES deposits in macrophages of the skin, liver, spleen, lung and kidney, but not in the CNS and the placenta (201). Tissue deposition of HES is dose-dependent, transitory and is greater in patients suffering from pruritus (202). HES deposition in cutaneous nerves may be a consequence of a higher cumulative dosage and can account for the pruritus (202). It usually ceases when HES deposits are released. In summary, the storage of HES in the small peripheral nerves suggests a cutaneous origin of HES-induced pruritus (201). Symptomatic relief may be received by topical capsaicin (203). Treatment of drug-induced pruritus entails immediate discontinuation of the offending agent.

PRURITUS IN NEUROPSYCHIATRIC DISORDERS

If onset of pruritus is temporally associated with significant psychopathology, such as anxiety, depression or schizophrenia, it may be called psychogenic pruritus. Some consider that this should remain a diagnosis of exclusion. Other causes of pruritus have to be carefully ruled out, but one could argue that an overlapping of physical and psychological causes is possible and severe pruritus itself may lead to psychological stress resulting in depression. Many patients experience impairment in social or occupational functioning. No primary lesions are seen, but secondary lesions ranging from lichenification to excoriations may be present.

Neurotic excoriations often result in deep, linear or punctate lesions with scarring. A diagnostic clue to the disease is sparing of the upper back, as this region is difficult to reach. Patients lack delusions of infection or infestation, but have an exaggerated response to minor irritation of the skin. Obsessive-compulsive disorder is a frequent cause of these types of behaviour (204).

Monosymptomatic hypochondriacal psychosis, otherwise known as delusions of parasitosis, is a condition in which patients have a false belief of infestation of the skin (46). Sufferers are usually middle-aged women and typically are rational in every other way. They may feel pruritic or crawling sensations and this tends to result in marked self-mutilation. Patients may bring shreds of tissue and skin as "proof" of their parasitosis. By definition, these patients do not respond to reasoning and pharmacologic therapy may be the only option.

Treatment of psychogenic pruritus varies with the underlying disorder, which itself may require referral to a psychiatrist. Anxiety disorders often respond to anxiolytics such as diazepam and buspirone. Delusional disorders respond well to neuroleptic medications such as haloperidol

Table VII. *Pathomechanisms in drug-induced pruritus*

Pathomechanism	Medication
1. Cholestasis	Valproic acid, Chloroform, oral contraceptives, minocycline
2. Hepatotoxicity	Oral contraceptives and other oestrogens Testosterone and other anabolic steroids Phenothiazine, Tolbutamide, Erythromycin, Azathioprine, Penicillamine
3. Sebostasis/Xerosis	Beta-blockers, Retinoids, Tamoxifen, Busulfan, Clofibrate
4. Phototoxicity	8-methoxypsoralen
5. Neurologic	Tramadol, Codeine, Cocaine, Morphine, Butorphanol, Fentanyl
6. Deposition	Hydroxyethyl starch
7. Idiopathic	Chloroquine, Clonidine, Gold salts, Lithium

and pimozide. Depression is increasingly being treated with selective serotonin uptake inhibitors because of their low side-effect profile, but traditional therapies such as tricyclic antidepressants remain useful (205). Clomipramine can be beneficial in obsessive-compulsive disorder.

VARIOUS

Brachioradial pruritus: Defined as a chronic, uncommon, intermittent pruritus of the flexor surface of the elbows, brachioradial pruritus remains an enigma. Solar damage over time, presence of a cervical rib or cervical nerve root impingement may be contributory factors (206, 207). A recent case report describes a spinal cord tumour as the cause of bilateral brachioradial pruritus (208). Interestingly, UV light exacerbates the condition and patients report remission in the fall and winter months of temperate climates. Examination may reveal excoriations localized to the vicinity of the brachioradialis muscle origin. However, dermatitis of the affected area is rare. Treatment options include non-steroidal anti-inflammatory drugs, topical capsaicin cream, physical therapy, cutaneous field stimulation (CFS) and acupuncture (207, 209).

Notalgia paraesthetica: This condition, first described by Astwazaturow in 1934, is characterized by focal, intense pruritus over the medial scapular borders and is occasionally accompanied by pain, paraesthesia, and/or hyperaesthesia (210). A characteristic finding on physical examination is a well-circumscribed hyperpigmented patch on the affected area. This is due to melanophages, which are evident on examination of a biopsy specimen, and is thought to be secondary to chronic rubbing and scratching of the pruritic area. The biopsy specimen can also contain amyloid. Various aetiologies have been reported, including heredity, increased dermal innervation and viscerocutaneous reflex mechanisms. More recent work has focused on the disease as a sensory neuropathy secondary to neurotoxic chemicals or dorsal spinal nerve trauma or entrapment – unfortunately with inconsistent electromyography results (211).

Topical capsaicin cream has been reported as successful (212). Other options include topical corticosteroids, lidocaine, cutaneous field stimulation (209) and an interesting single case report of paravertebral block at spinal levels T3–T6 with bupivacaine and methylprednisolone acetate resulting in 12 symptom-free months (213).

PRURITUS THERAPY

Thus far, there is no specific anti-pruritic drug that parallels aspirin's association with pain relief. In the setting of pruritus, each patient and disease has to be seen as unique, and there are no therapies that work for all patients (46). The currently available therapeutic options have been included in each section for better understanding.

General therapy

The therapy of pruritus has several categories, all of them emphasizing the cause, which means identification and treatment of the underlying disease. Symptomatic treatment includes topical treatment, systemic treatment and physical treatment modalities such as phototherapy, electronic or thermal counterstimulation (e.g. itch stopper). Information given to patients about eliminating provocative factors should comprise the following:

- Wear appropriate clothing (no wool or synthetic fabrics; instead cotton clothing).
- Avoid excessive bathing; therefore take warm (not cold, not hot), short-lasting showers with non-drying detergents such as bath oil implemented. Colloid or tar or potassium permanganate baths for 10 to 15 min may be helpful.
- Hydrate the skin regularly on a daily basis with non-specific topical preparations. Emollients should be selected individually depending on the patient's skin condition and in consideration of the patient's compliance. Rich emollients may be used at night, whereas creams are more appropriate for daytime use in enabling the patient to wear clothing without any restriction.
- Follow advice concerning adequate methods of how to interrupt the itch-scratch cycle, such as application of a cold wash cloth, gentle pressure, etc.
- Take controlled physical exercise (28).
- Avoid stress and anxiety.
- Avoid coming into contact with dust and dust mites.
- Avoid heat, hot foods, hot drinks and other hot liquids.
- Take part in relaxation therapy.

Topical treatment

Topical treatment encompasses the application of non-specific emollients on a regular daily basis in order to prevention dryness and xerosis of the skin leading to pruritus. A large variety of topical compounds with antipruritic potency are currently available (Table VIII).

Topical anaesthetic agents decrease pain and pruritic sensation and may greatly relieve tingling and dysaesthesia. The onset of action is usually fast, but the duration is limited. No comparative studies clearly demonstrate any one agent as being superior to any other (46). Early preparations such as lignocaine are less effective, because these do not penetrate the stratum corneum well. EMLA (ligno-

Table VIII. *Topical treatment modalities*

-Emollients
-Corticosteroids: group I to VII potency
-Coal tar: gels, shampoos, bath additives, solution, cream, ointment
-Cooling agents: shake lotions (e.g. calamine, alcohol)
-Anaesthetics: benzocaine, lidocaine, prilocaine/lidocaine, pramoxine
-Antihistamine: diphenhydramine, dimetindene, promethazin, doxepin
- Miscellaneous: Camphor, Menthol, Capsaicin, Tacrolimus, Crotamiton, Pimecrolimus and others

caine/-prilocaine cream) has shown antipruritic potency in experimentally induced pruritus and may be sufficient in localized pruritic states such as notalgia paraesthetica (29). Effectiveness can be improved by combining an anaesthetic with urea, also known for its antipruritic potency (29). The therapeutic effect depends on the underlying disease (e.g. no therapeutic benefit was seen in AD) (30). Benzocaine, lidocaine and similar anaesthetics are likely to be more potent antipruritic agents than pramoxine, menthol and camphor (46).

The topical antihistamine dimethindene may improve pruritus severity (29) depending on the underlying cause as no effect was seen in AD (30). Doxepin has demonstrated modest antipruritic effects in AD and other eczematous dermatoses such as lichen simplex chronicus, nummular eczema and contact dermatitis (214, 215). Promethazine, too, has antipruritic potency, most likely due to antihistaminergic activity (46). Diphenhydramine is widely used in the USA, despite no controlled studies having proved its antipruritic potency (46). Side effects such as drowsiness and xerostomia occur when large parts of the body are covered and young children are treated. Intoxications have been reported with promethazine (46). With doxepin, an increased risk of allergic contact dermatitis needs to be considered (216).

Capsaicin is a naturally occurring alkaloid found in many botanical species of the night shade family (solanacea) including the pepper plants. Capsaicin enhances the release and secondarily inhibits the reaccumulation of neuropeptides such as substance P, one of the most powerful vasodilators releasing histamine from cutaneous mast cells by an indirect effect and inducing plasma extravasation by a direct effect on the small skin blood vessels. According to a recent study (217), hypalgesia produced by capsaicin results from the degeneration of epidermal nerve fibres. Discontinuation of capsaicin was followed by reinnervation of the epidermis with a return of all sensations such as tactile, mechanical, heat and pain sensations except cold.

Topical capsaicin therapy has been reported as being successful in various dermatologic disorders (Table IX), but in patients with AD the results have been controversial (32). Available concentrations range from 0.025% to 0.3% and need to be applied 3 to 5 times daily for maximum effect. It has been shown to be a safe treatment even on large skin areas (161). Side effects include stinging, burning, pain, erythema and irritation, all of which decrease with continued use.

Tacrolimus is a macrolide agent and exerts its effects by inhibiting T-lymphocyte activation in a fashion similar to the macrolide cyclosporine, but is approximately 100 times more potent than cyclosporine. It is substantially smaller, which allows for greater percutaneous penetration. Tacrolimus reduces pruritus via the modulation and suppression of T-cell invasion and mediators that can provoke pruritus. Controlled trials indicate that topical tacrolimus is a safe and efficient treatment in AD, showing rapid anti-inflammatory and antipruritic effects (218). Long-term safety appears superior to corticosteroid agents. Burning, pruritus and erythema are the most commonly reported application-site adverse events (218).

Pimecrolimus (SDZ ASM 981) is the first ascomycin macrolactam derivative developed for the treatment of inflammatory skin diseases. It selectively inhibits pro-inflammatory cytokines from T cells and mast cells in vitro. In a recent controlled study, an improvement of pruritus in patients with AD was noted (94). Pimecrolimus is likely to be less effective than tacrolimus in decreasing the pruritus of inflammatory diseases. Side effects are burning and application-site pruritus.

Table IX. *Indications for topical capsaicin therapy*

Effect confirmed in controlled clinical trials:
- (Chronic) postherpetic neuralgia (243)
- Diabetic neuropathy (244)
- Post-mastectomy pain syndrome (245)
- Notalgia paraesthetica (212)
- Haemodialysis-related pruritus (161,162)
- Brachioradial pruritus (207)
- Pruritic psoriasis (246, 247)

Effect confirmed in case series or case reports:
- Peripheral pain (248)
- Aquagenic pruritus (107)
- Prurigo nodularis (103, 249, 250)
- Chronic prurigo (250)
- Lichen simplex chronicus (249, 250)
- Nummular eczema (249)
- Hydroxyethyl starch-induced pruritus (203, 249)
- Apocrine chromohydrosis (251)
- PUVA associated pruritus (252)
- Pityriasis rubra pilaris related pruritus (253)

Whereas systemic aspirin does not have any antipruritic effect (219, 220), topical application of an aspirin/dichloromethane solution has indicated a significant antipruritic potency in patients suffering from localized circumscribed pruritus, such as occurs in lichen simplex chronicus (221). A possible mechanism could be a peripheral nociceptive effect of salicylic acid on pruritus (221). Other studies have not confirmed this in detail in a human experimental model (42).

Crotamiton is an effective scabicide. There have been anecdotal reports by some patients that this agent is highly effective in ameliorating pruritus. A double-blind study did not show a significant antipruritic potency of crotamiton lotion compared to its vehicle (46).

Topical application of *strontium nitrate* reduced the magnitude and duration of histamine-induced pruritus significantly (222). The mechanism is unclear, but may be due to a direct effect on the C fibres. Further investigations will show whether strontium nitrate might also be useful in clinical dermatology.

Zangrado, an extract of the Amazonian ethnomedicine Sangre de Grado, showed antipruritic, anti-inflammatory and analgetic effects when topically applied in a placebo-controlled study. These actions appear to be mediated by vanilloid receptor antagonism (223). This substance may offer significant therapeutic potential in the future.

Systemic treatment

Most drugs with antipruritic potency act centrally by a property or mechanism related to sedation. Placebo responses in pruritus are fairly marked and were achieved in 66% of patients in one study (224). Many systemic drugs with antipruritic effects may work primarily by placebo mechanism, demonstrating the powerful central nervous modulation of pruritus. Some neurotropic and psychotropic drugs can be used in the treatment of pruritus (225). A brief summary of systemic drugs with antipruritic potency and their mechanisms of action is given in Table X.

Serotonin receptor antagonists of the 5-HT$_3$ type have been reported with variable success in the treatment of uraemic, hepatic, opioid-induced pruritus and pruritus in cancer (32, 152, 153, 157, 179, 226–228). The wide variation in study design restricts the potential for meta-analysis. Another problem is the wide variation in the bioavailability of serotonin receptor antagonists of the 5-HT$_3$ type through variable absorption between individuals, route

Table X. *Systemic drugs with antipruritic potency*

Drug	Mechanisms	Possible indication
H$_1$-antihistamines	Histamine receptor-1 blockade	Urticaria, angioedema
First generation	Sedation by blockade of central and peripheral muscarinic receptors	Atopic dermatitis Various eczematous diseases
2nd, 3rd gen	Peripheral activity Anti-inflammatory	
H$_2$-antihistamines	Histamine receptor-2 blockade	Polycythaemia rubra vera enhancing therapeutical effect of H$_1$ blockers (90)
Doxepin	H$_1$, H$_2$, H$_3$ receptor blockade Antimuscarinic, -serotoninergic, -alpha-adrenergic activity	Neurogenic or psychogenic itch Neurotic excoriation (225)
Glucocorticosteroids	Reduction of access of inflammatory cells by affection of lymphocyte and monocyte function	Inflammatory skin diseases, for example contact dermatitis, photodermatitis erythroderma, bullous pemphigoid (254)
Cyclosporin	Inhibition of lymphokine production	Atopic dermatitis, psoriasis, bullous disorders (255)
Thalidomide	Anti-inflammation Immunomodulation	Prurigo nodularis, HIV, psoriasis, actinic prurigo, senile pruritus, actinic prurigo, senile pruritus, renal diseases, primary biliary cirrhosis, lichen simplex chronicus (158, 192, 193, 256)
Naloxone Naltrexone Nalmefene	Opioid receptor antagonist (μ-receptor)	Cholestasis, primary biliary cirrhosis, renal diseases (?), pruritus in various dermatoses (93)
TRK-820	(κ-receptor)	?(63)
Ondansetron	5-HT3 receptor antagonist	Cholestasis, renal diseases (?), opioid application (not prophylactic) (257)
Paroxetine	Selective serotonin reuptake inhibitor	Psychogenic and neurotic excoriations (205) Pruritus in advanced cancer (258) Polycythaemia vera (178)

of administration and dose prescribed. In summary, a role for serotonin receptor antagonists in different types of pruritus, such as for example renal pruritus, appears unlikely, but cannot definitely be excluded. A recent publication warns of the serotonin syndrome, because two cases occurred when serotonin receptor antagonists of the 5-HT$_3$ type were applied in chemotherapy induced nausea in combination with other drugs such as mirtazapine and fentanyl (229). Perhaps, blocking one type of serotonin receptor and functionally increasing systemic and CNS levels of serotonin simultaneously, hence presenting excessive serotonin to other receptors, increases the risk of serotonin syndrome (229). Application of 5-HT$_3$ receptor antagonists may pose a potential risk when used in severely ill patients with multidrug therapy, especially in centrally acting substances.

Experiments in animals suggest that the κ-opioid receptor modulates the perception of itch. TRK-820 is a newly synthesized κ-opioid receptor-selective agonist that has shown antipruritic activity in antihistamine-sensitive and -resistant pruritus in an animal model (63). This substance may represent a new entity of drugs for treating pruritus in humans, but further investigation is necessary.

Physical treatment modalities

Ultraviolet light (UVA, UVB, UVA/UVB) and PUVA therapy have shown most benefit in inflammatory dermatoses, pruritus related to uraemia, primary biliary cirrhosis, polycythaemia rubra vera and prurigo nodularis.

Transcutaneous electronic nerve stimulation (TENS) has been reported as beneficial in types of pruritus such as that found in aged skin, but not sufficient for practical clinical purposes (230). The effect may be a partial placebo effect, as it tends to decline with continued therapy (46). Cutaneous field stimulation is a new technique stimulating thin afferent fibres including C-fibres (209, 230). In a recent open-label uncontrolled study, patients with localized itching experienced sufficient relief. Skin biopsies showed that the number of epidermal nerve fibres was reduced in parallel with the relief of itch. Patients with generalized pruritus did not have any benefit. It is suggested that cutaneous field stimulation acts through endogenous central inhibitory mechanisms that are normally activated by scratching the skin (230). Interestingly, single and repeated cutaneous field stimulation treatments reduce the itch sensation but do not have any beneficial effects on contact dermatitis (231).

Acupuncture has been reported as successful in the treatment of pruritus vulvae, allergic contact dermatitis and renal pruritus (46). According to reports, acupuncture decreases experimental histamine-induced pruritus, but has no effect on maximal pruritus intensity and onset time (232).

Psychological approaches

It has become increasingly clear that psychological factors can affect the course of any physical disease process (1). Pruritus may be precipitated, prolonged or enhanced by a number of stress-related mediators such as histamine and neuropeptides. It has to be borne in mind that there are a number of secondary psychosomatic mechanisms through which pruritus may be generated or exacerbated, e.g. sweat response, alterations in cutaneous blood flow and scratching (1).

Studies show that group psychotherapy, behavioural therapy, controlled physical exercise, support groups and biofeedback help to stop scratching and improve quality of life (1, 28, 46).

SUMMARY AND CONCLUSIONS

Pruritus is a primary sensory modality that has been recognized since antiquity; it is the most frequently described symptom in dermatology. Dermatologic diseases and systemic diseases can lead to this non-specific symptom, and thorough physical examination and laboratory study evaluation of patients may lead clinicians to a specific aetiology. Objective measures of pruritus severity, scratching severity and the impact of pruritus on quality of life are evolving fields.

Itch receptors have been identified as free unmyelinated nerve endings with extensive arborization occurring in the epidermis of the skin, the mucous membrane and the cornea. CNS control centres modulate pruritus sensations, and may be responsible for contributing to the pathogenesis of select pruritic condition. Many mediators have been identified, including histamine, neuropeptides, opioids, cytokines and others. Because no single mechanism or mediator is responsible for all pruritus, no single therapeutic approach will work for all pruritic conditions.

Thus far, there is no specific anti-pruritic drug that parallels the ability of aspirin to relieve pain. In the setting of pruritus, each patient and disease should be seen as unique and that there are no therapies that work for all patients. Patient education and elimination of provocative factors are always significant, and many patients benefit from topical treatments ranging from moisturizers to topical anaesthetics, macrolide immunomodulators and capsaicin. A wide variety of systemic agents may be efficacious, and select patients benefit from physical treatment modalities.

REFERENCES

1. Bernhard JD. Itch: Mechanisms and management of pruritus. McGraw Hill, New York, 1994.
2. Zirwas MJ, Seraly MP. Pruritus of unknown origin: A retrospective study. J Am Acad Dermatol 2001; 45: 892–896.

3. Pujol RM, Gallardo F, Llistosella E, Blanco A, Bernadó L, Bordes R, et al. Invisible mycosis fungoides: A diagnostic challenge. J Am Acad Dermatol 2002; 47: S168–171.
4. Liddell K. Hippocrates of Cos (460-377 BC). Clin Exp Dermatol 2000; 25: 86–88.
5. Hafenreffer S. De pruriti, in Nosodochium, in quo cutis, eiqe adhaerentium partium, affectus omnes, singulari methodo, et cognoscendi et curandi fidelissime traduntur. Ulm, B Kuehn, 1660, 98–102.
6. Dotz W. Jean Paul Marat. His life, cutaneous disease, death, and depiction by Jacques Louis David. Am J Dermpath 1979; 3: 247–250.
7. Appleyard OB. Jean-Paul Marat (1743-1793) – Revolutionary and doctor of medicine. Practitioner 1971; 206: 826–835.
8. Jelinek JE. Jean-Paul Marat – The differential diagnosis of his skin disease. Am J Dermpath 1979; 3: 251–252.
9. Murphy LC. The itches of Jean-Paul Marat. J Am Acad Dermatol 1989; 21: 565–567.
10. Baer RL. Historical overview of the evolution of investigative dermatology (1775-1993). J Invest Dermatol 1994; 103: 3-6.
11. Schmelz M. A neural pathway for itch. Nat Neurosci 2001; 4: 9-10.
12. Andrew D, Craig AD. Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. Nat Neurosci 2001; 4: 72–77.
13. Arthur RP, Shelley WB. The innervation of human epidermis. J Invest Dermatol 1959; 32: 397–411.
14. Dalsgaard CJ, Rydh M, Haegerstrand A. Cutaneous innervation in man visualized with protein gene product 9.5 (PGF 9.5) antibodies. Histochemistry 1989; 92: 385–389.
15. Wang L, Hilliges M, Jernberg T, Wiegleb-Edstrom D, Johannson O. Protein gene product 9.5-immunoreactive nerve fibers and cells in human skin. Cell Tissue Res 1990; 261: 25–33.
16. Kennedy WR, Wendelschafer-Crabb G. The innervation of the human epidermis. J Neurosci 1993; 115: 184–190.
17. Rumio C, Castano P, Veraldi S, Morini M, Castano SM. The innervation of human skin studied with confocal scanning laser microscopy: A comparison between PGP 9.5 immunofluorescence and silver impregnations. Neuroimage 1995; 2: 102–111.
18. Kawakami T, Ishihara M, Mihara M. Distribution density of intraepidermal nerve fibers in normal human skin. J Dermatol 2001; 63–70.
19. Wahlgren CF, Ekblom A. Two-point discrimination of itch in patients with atopic dermatitis and healthy volunteers. Acta Derm Venereol 1996; 76: 48–51.
20. Ruckwied R, Zeck S, Schmelz M, McGlone F. Sensitivity of human scalp investigated by intradermal microdialysis in vivo. J Am Acad Dermatol 2002; 47: 245–250.
21. Schmelz M, Schmid R, Bickel A, Handwerker HO, Torebjörk HE. Specific C-receptors for itch in human skin. J Neurosci 1997; 17: 8003–8008.
22. Ekblom A. Some neurophysiological aspects of itch. Sem Dermatol 1995; 14: 262–270.
23. Hsieh JC, Hägermark Ö, Ståhle-Bäckdahl M, Ericson K, Erikson L, Stone-Elander S, Ingvar M. Urge to scratch represented in the human cerebral cortex during itch. J Neurophysiol 1994; 72: 3004–3008.
24. Drzezga A, Darsow U, Treede RD, Siebner H, Frisch M, Munz F, et al. Central activation by histamine-induced itch: analogies to pain processing: a correlation analysis of O-15 H_2O positron emission tomography studies. Pain 2001; 92: 295–305.
25. Bickford RG. Experiments relating to the itch sensation. Its peripheral mechanisms, and central pathways. Clin Sci 1938; 3: 377–386.
26. Simone DA, Alreja M, LaMotte BH. Psychophysical studies of the itch sensation and itchy skin ("alloknesis") produced by intracutaneous injection of histamine. Somatosens Mot Res 1991; 8: 271–279.
27. Heyer G, Dotzer M, Diepgen TL, Handwerker HO. Opiate and H1 antagonist effects on histamine induced pruritus and alloknesis. Pain 1997; 73: 239–243.
28. Heyer GR, Hornstein OP. Recent studies of cutaneous nociception in atopic and non-atopic subjects. J Dermatol 1999; 26: 77–86.
29. Weisshaar E, Heyer G, Forster C, Hornstein OP, Handwerker HO. Effects of topical antihistamine and topical anaesthetics on iontophoretically induced itch. Hautarzt 1996; 47: 355–360.
30. Weisshaar E, Forster C, Dotzer M, Heyer G. Experimentally induced pruritus and cutaneous reaction with topical antihistamine and local analgesics in atopic eczema. Skin Pharmacol 1997; 10: 183–190.
31. Weisshaar E, Heyer G, Forster C, Handwerker HO. Effect of topical capsaicin on the cutaneous reactions and itching to histamine in atopic eczema compared to healthy skin. Arch Dermatol Res 1998; 290: 306–311.
32. Weisshaar E, Ziethen B, Gollnick H. Can a serotonin type 3 (5-HT3) receptor antagonist reduce experimentally-induced itch? Inflam Res 1997; 46: 412–416.
33. LaMotte BH. Subpopulations of 'nocifensor neurons' contributing to pain, allodynia and alloknesis. Am Pain Soc J 1992; 1: 115–126.
34. Handwerker HO. Pain and allodynia, itch and alloknesis: an alternative hypothesis. Am Pain Soc J 1992; 1: 135–138.
35. Heyer G, Groene D, Martus P. Efficacy of naltrexone on acetylcholine-induced alloknesis in atopic eczema. Exp Dermatol 2002; 11: 448–455.
36. Bernhard JD. Nonrashes 5. Atmoknesis: Pruritus provoked by contact with air. Cutis 1989; 44: 143–144.
37. Pintér E, Szolcsányi J. Plasma extravasation in the skin and the pelvic organs evoked by antidromic stimulation of the lumbosacral dorsal roots of the rat. Neurosci 1995; 68: 603–614.
38. Schmelz M, Zeck S, Raithel M, Rukwied R. Mast cell tryptase in dermal neurogenic inflammation. Clin Exp Allergy 1999; 29: 695–702.
39. Lewis T, Harris KE, Grant RT. Observations relating to the influence of the cutaneous nerves on various reactions of the cutaneous vessels. Heart 1927; 14: 1–17.
40. Rukwied R, Lischetzki G, McGlone F, Heyer G, Schmelz M. Mast cell mediators other than histamine induce pruritus in atopic dermatitis patients: a dermal microdialysis study. Br J Dermatol 2000; 142: 1114–1120.
41. Hägermark Ö. Peripheral and central mediators of itch. Skin Pharmacol 1992; 5: 1–8.
42. Thompsen JS. Itch models and effect of topical antipruritic substances. Forum for Nord Derm Ven 2002; 7(suppl.5):7–42.
43. Fjellner B, Hägermark Ö. Pruritus in polycythaemia: treatment with aspirin and possibility of platelet involvement. Acta Derm Venereol 1979; 59: 505–512.
44. Beck PW, Handwerker HO. Bradykinin and serotonin effects on various types of cutaneous nerve fibers. Pflügers Arch 1974; 347: 209–222.
45. Lischetzki G, Rukwied R, Handwerker HO, Schmelz M. Nociceptor activation and protein extravasation induced by inflammatory mediators in human skin. Eur J Pain 2001; 5: 49–57.

46. Fleischer AB. The clinical management of itching. Parthenon Publishing, New York, London, 2000.

47. Holzer P. Neurogenic vasodilation and plasma leakage in the skin. Gen Pharmacol 1988; 30: 5–11.

48. Scholzen T, Armstrong CA, Bunnett LW, Luger TA, Olerud JE, Ansel JC. Neuropeptides in the skin: interactions between the neuroendocrine and the skin immune system. Exp Dermatol 1998; 7: 81–96.

49. Hägermark Ö, Hokfelt T, Pernow B. Flare and itch induced by substance P in human skin. J Invest Dermatol 1978; 71: 233–235.

50. Weidner C, Klede M, Rukwied R, Lischetzki G, Neisius U, Skov PS, et al. Acute effects of substance P and calcitonin gene-related peptide in human skin – a microdialysis study. J Invest Dermatol 2000; 115: 1015–1020.

51. Henry JL. Substance P and inflammatory pain: potential of substance P antagonists and analgesics. Agents Actions Suppl 1993; 41: 75–87.

52. Osterle LS, Cowen T, Rustin MH. Neuropeptides in the skin of patients with atopic dermatitis. Clin Exp Dermatol 1995; 26: 462–467.

53. Andoh T, Nagasawa T, Satoh M, Kuraishi Y. Substance P induction of itch-associated response mediated by cutaneous NK1 tachykinin receptors in mice. J Pharmacol Exp Ther 1998; 286: 1140–1145.

54. Toyoda M, Nakamura M, Makino T, Hino T, Kagoura M, Morohashi M. Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. Br J Dermatol 2002; 147: 71–79.

55. Ständer S, Gunzer M, Metze D, Luger T, Steinhoff M. Localization of μ-opioid receptor 1A on sensory nerve fibers in human skin. Regul Pept 2002; 110: 75–83.

56. Königstein H. Experimental study of itch stimuli in animals. Arch Dermatol Syphiol 1948; 828–849.

57. Feldberg W, Sherwood SL. Injections of drugs into the lateral ventricle of the cat. J Physiol 1954; 123: 148–168.

58. Bergasa NV, Thomas DA, Vergalla J, Turner ML, Jones EA. Plasma from patients with the pruritus of cholestasis induces opioid receptor-mediated scratching in monkeys. Life Sci 1993; 53: 1253–1257.

59. Yeh HM, Chen LK, Lin CJ, Chan WH, Chen YP, Lin CS, et al. Prophylactic intravenous ondansetron reduces the incidence of intrathecal morphine-induced pruritus in patients undergoing cesarean delivery. Anesth Analg 2000; 91: 172–175.

60. Scott PV, Fischer HBJ. Intraspinal opiates and itching: a new reflex? BMJ 1982; 284: 1015–1016.

61. Milner AR, Bogad DG. Intrathecal administration of morphine for elective cesarean section. Anesthesia 1996; 51: 871–873.

62. Swart M, Sewell J, Thomas D. Intrathecal administration for elective cesarean section: an assessment of pain relief, satisfaction, and side effects. Anesthesia 1997; 52: 373–377.

63. Togashi Y, Umeuchi H, Okano K, Ando N, Yoshizawa Y, Honda T, et al. Antipruritic activity of the κ-opioid receptor agonist, TRK-820. Eur J Pharmacol 2002; 435: 259–264.

64. Georgala S, Schulpis KH, Papaconstantinou ED, Stratigos J. Raised beta-endorphin serum levels in children with atopic dermatitis and pruritus. J Dermatol Sci 1994; 8: 125–128.

65. Mettang T, Fischer FP, Dollenbacher U, Kuhlmann U. Uremic pruritus is not related to beta-endorphin serum levels in hemodialysis patients. Nephrol Dial Transplant 1998; 13: 231–232.

66. Bergasa NV. Pruritus and fatigue in primary biliary cirrhosis. Baillières Clin Gastroenterol 2000; 14: 643–655.

67. DeHaven-Hudkins DL, Cowan A, Cortes Burgos L, Daubert JD, Cassel JA, DeHaven RN, et al. Antipruritic and antihyperalgesic actions of loperamide and analogs. Life Sci 2002; 71: 2787–2796.

68. Wahlgren CF, Scheynius A, Hägermark Ö. Antipruritic effect of oral cyclosporin A in atopic dermatitis. Acta Derm Venereol 1990; 70: 323–329.

69. Wahlgren CF. Pathophysiology of itching in urticaria and atopic dermatitis. Allergy 1992; 47: 65–75.

70. Gaspari AA, Lotze MT, Rosenberg SA, Stern JB, Katz SI. Dermatologic changes associated with interleukin-2 administration. JAMA 1987; 258: 1624–1629.

71. Wahlgren CF, Tengvall Linder M, Hägermark Ö, Scheynius A. Itch and inflammation induced by intradermally injected interleukin-2 in atopic dermatitis patients and healthy subjects. Arch Dermatol Res 1995; 287: 572–580.

72. Darsow U, Scharein E, Bromm B, Ring J. Skin testing in the pruritogenic activity of histamine and the cytokines (interleukin-2 and tumor necrosis factor-alpha) at the dermal-epidermal junction. Br J Dermatol 1997; 137: 415–417.

73. Lippert U, Hoer A, Möller A, Ramboer I, Cremer B, Henz BM. Role of antigen-induced cytokine release in atopic pruritus. Int Arch Allergy Immunol 1998; 116: 36–39.

74. Mettang T, Pauli-Magnus C, Alscher DM. Uraemic pruritus – new perspectives and insights from recent trials. Nephrol Dial Transplant 2002; 17: 1558–1563.

75. Lober C. Should the patient with generalized pruritus be evaluated for malignancy? J Am Acad Dermatol 1988; 19: 350–352.

76. Ståhle-Bäckdahl M. Uremic pruritus: clinical and experimental studies. Acta Derm Venereol 1989; Suppl 145: 1–38.

77. Wahlgren CF, Ekblom A, Hägermark Ö. Some aspects of the experimental induction and measurement of itch. Acta Derm Venereol 1989; 69: 185–189.

78. Melin L, Frederikson T, Noren P, Swebilius BG. Behavioural treatment of scratching in patients with atopic dermatitis. Br J Dermatol 1986; 115: 467–474.

79. Felix R, Shuster S. A new method for the measurement of itch and the response to treatment. Br J Dermatol 1975; 93: 303–312.

80. Ebata T, Iwasaki S, Kamide R, Niimura M. Use of a wrist activity monitor for the measurement of nocturnal scratching in patients with atopic dermatitis. Br J Dermatol 2001; 144: 305–309.

81. Yosipovitch G, Zucker I, Boner G, Gafter U, Shapira Y, David M. A questionnaire for the assessment of pruritus: validation in uremic patients. Acta Derm Venereol 2001; 81: 108–111.

82. Yosipovitch G, Goon A, Wee J, Chan YH, Goh CL. The prevalence and clinical characteristics of pruritus among patients with extensive psoriasis. Br J Dermatol 2000; 143: 969–973.

83. Yosipovitch G, Ansari N, Goon A, Chan YH, Goh CL. Clinical characteristics of pruritus in chronic idiopathic urticaria. Br J Dermatol 2002; 147: 32–36.

84. Yosipovitch G, Goon AT, Wee J, Chan YH, Zucker I, Goh CL. Itch characteristics in Chinese patients with atopic dermatitis using a new questionnaire for the assessment of pruritus. Int J Dermatol 2002; 41: 212–216.

85. Darsow U, Mautner VF, Bromm B, Scharein E, Ring J. The Eppendorf Itch Questionnaire. Hautarzt 1997; 48: 730–733.

86. Darsow U, Scharein E, Simon D, Walter G, Bromm B, Ring J. New aspects of itch pathophysiology: component analysis of atopic itch using the "Eppendorf Itch Questionnaire". Int Arch Allergy Immunol 2001; 124: 326–331.

87. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980; suppl 92: 44–47.
88. Thestrup-Pedersen K. Clincal aspects of atopic dermatitis. Clin Exp Dermatol 2000; 25: 535–543.
89. Wahlgren CF. Itch and atopic dermatitis: clinical and experimental studies. Acta Derm Venereol 1991; Suppl 165: 4–53.
90. Greaves MW. Antihistamines. Derm Clin 2001; 19: 53–62.
91. Krause L, Shuster S. Mechanism of action of antipruritic drugs. BMJ 1983; 287: 1199–1200.
92. Klein PA, Clarke RAF. An evidence-based review of the efficacy of antihistamine in relieving pruritus in atopic dermatitis. Arch Dermatol 1999; 135: 1522–1525.
93. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological disease. J Am Acad Dermatol 1999; 41: 533–539.
94. Luger T, Van Leent EJM, Graeber M, Hedgecock S, Thurston M, Kandra A, et al. SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. Br J Dermatol 2001; 144: 788–794.
95. Reitamo S, Ansul JC, Luger TA. Itch in atopic dermatitis. J Am Acad Dermatol 2001; 45: S 55–56.
96. Ständer S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. Exp Dermatol 2002; 11: 12–24.
97. Barker DJ. Generalized pruritus as the presenting feature of bullous pemphigoid. Br J Dermatol 1983; 109: 237–239.
98. Bingham EA, Burrow D, Sanford JC. Prolonged pruritus and bullous pemphigoid. Clin Exp Dermatol 1984; 9: 564–570.
99. Gupta MA, Gupta AK, Kirby S, Weiner HK, Mace TM, Schork NJ, et al. Pruritus in psoriasis. A prospective study of some psychiatric and dermatologic correlates. Arch Dermatol 1988; 124: 1052–1057.
100. Sehgal VN, Bajaj P, Jain S. Pityriasis rubra pilaris (PRP): report of four cases. J Dermatol 2000; 27: 174–177.
101. Griffith WAD. Pityriasis rubra pilaris: clinical features and natural history in a study of 93 patients. Br J Dermatol 1977; 97 (suppl 15): 18.
102. Accioly-Filho LW, Nogueira A, Ramos-e-Silva M. Prurigo nodularis of Hyde: an update. J Eur Acad Dermatol Venereol 2000; 14: 75–82.
103. Ständer S, Luger T, Metze D. Treatment of prurigo nodularis with topical capsaicin. J Am Acad Dermatol 2001; 44: 471–478.
104. Wong SS. Double-blind, right/left comparison of calcipotriol ointment and betamethasone ointment in the treatment of prurigo nodularis. Arch Dermatol 2000; 136: 807–808.
105. Potasman I, Heinrich I, Bassan HM. Aquagenic pruritus, prevalence and clinical observations. Isr J Med Sci 1990; 26: 499–503.
106. Menage HP, Greaves MW. Aquagenic pruritus. Sem Dermatol 1995; 14: 313–316.
107. Lotti T, Teofoli P, Tsampau D. Treatment of aquagenic pruritus with topical capsaicin cream. J Am Acad Dermatol 1994; 30: 232–335.
108. Moritz DL, Elmets CA. Eosinophilic pustular folliculitis. J Am Acad Dermatol 1991; 24: 903–907.
109. Nagashima M. Prurigo pigmentosa: clinical observation of our 14 cases. J Dermatol 1978; 5: 61–67.
110. Yazawa N, Ihn H, Yemane K, Etoh T, Tamaki K. The successful treatment of prurigo pigmentosa with macrolide antibiotics. Dermatology 2001; 202: 67–69.
111. Schwartz ME. Barn itch. Am Fam Phys 1983; 27: 149–153.
112. Daye S, McHenry JA, Rosceeli JD. Pruritic rash associated with cat scratch disease. Pediatrics 1988; 81: 559–561.
113. Lamberg DI, Green S. Status report of 376 mycosis fungoides patients at 4 years: Mycosis fungoides cooperative group. Cancer Treat Rep 1979; 63: 701–707.
114. Fleischer AB Jr. Pruritus in the elderly. From: Advances in Dermatology, Mosby 1995: 41–59.
115. Malott KR, Stedinger SL. Pruritus. In: Geriatric Dermatology. Igaku-Shoin Medical Publishers, Inc NY, NY 1989: 207–226.
116. Kimyai-Asadi A, Nousari HC, Kimyai-Asadi T, Milani F. Poststroke pruritus. Stroke 1999; 30: 692–693.
117. Daniel GL, Longo WE, Vernava AM. Pruritus ani. Causes and concerns. Dis Colon Rectum 1994; 37: 670–674.
118. Lochridge E. Pruritis ani – perianal psoriasis. South Med J 1969; 62: 450–452.
119. Dasan S, Neill SM, Donaldson DR, Scott HJ. Treatment of persistent pruritus ani in a combined colorectal and dermatological clinic. Br J Surg 1999; 86: 1337–1340.
120. Raddin JB. Pruritus ani, a diagnostic test and indicated medication. Med Times 1961; 89: 687–689.
121. Rumpianski R, Shiskin J. Pruritus vulvae: A five year survey. Dermatologica 1965; 131: 146.
122. Bernhard JD. Macular amyloidosus, notalgia paresthetica and pruritus: Three sides of the same coin? Dermatologica 1991; 183: 53–56.
123. Weinstein BR, Bernhard JD. Incarceration for excoriation. Cutis 1990; 46: 240.
124. Wong TW, Lee JY, Sheu HM, Chao SC. Relief of pain and itch associated with keloids on treatment with oxpentifylline. Br J Dermatol 1999; 140: 771–772.
125. Vitale M, Fields-Blache C, Luterman A. Severe itching in the patients with burns. J Burn Care Rehabil 1991; 12: 330–333.
126. Phillips L, Robson M. Comments from Detroit Receiving Hospital, Detroit, Michigan. J Burn Care Rehabil 1988; 9: 308–309.
127. Bell C, McAdams T, Morgan R, Parshley P, Pike R, Riggs P, Carpenter JE. Pruritus in burns: a descriptive study. J Burn Care Rehabil 1988; 9: 305–308.
128. Matheson JD, Clayton J, Muller MJ. The reduction of itch during burn wound healing. J Burn Care Rehabil 2001; 22: 76–81.
129. Kopecky EA, Jacobson S, Hubley P, Palozzi C, Clarke HM, Koren G. Safety and pharmacokinetic of EMLA in the treatment of postburn pruritus in pediatric patients: A pilot study. J Burn Care Rehabil 2001; 22: 235–242.
130. Gilchrest BA, Stern RS, Steinman TI, Brown R, Arendt K, Anderson W. Clinical features among patients undergoing maintenance hemodialysis. Arch Dermatol 1982; 118: 154–156.
131. Ponticelli C, Bencini PL. Uremic pruritus: A review. Nephron 1992; 60: 1–5.
132. Dimkovic N, Djukanovic L, Radmilavic A, Bojic P, Juloski T. Uremic pruritus and skin mast cells. Nephron 1992; 61: 5–9.
133. Szepietowski J, Thepen T, van Vloten WA, Szepietowski T, Biharia JC. Pruritus and mast cell proliferation in the skin of hemodialysis patients. Inflam Res 1995; 44, suppl 1: S 84–85.
134. Neiman RS, Bischel MD, Lukes RJ. Uremia and mast-cell proliferation. Lancet 1972; 29: 959.
135. Matsumoto M, Ischimaru K, Horie A. Pruritus and mast cell proliferation of the skin in end stage renal failure. Nephron 1985; 23: 285–288.
136. Dallapiccola B, Tataranni G, Farinelli A. Uraemia and mast-cell proliferation. Lancet 1972; 1: 1231.

137. Klein LR, Klein JB, Hanno R, Callen JP. Cutaneous mast cell quantity in pruritic and non-pruritic hemodialysis patients. Int J Dermatol 1988; 27: 557–559.

138. Cohen EP, Russel TJ, Garancis JC. Mast cells and calcium in severe uremic itching. Am J Med Sci 1992; 303: 360–365.

139. Mettang T, Fritz P, Weber J, Machleidt C, Hütel E, Kuhlmann U. Uremic pruritus in patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). The role of plasma histamine and skin mast cells. Clin Nephrol 1990; 34: 136–141.

140. DeFilippi C, Regazzini R, Piazza V, Galli F, Pisati P, Sacchi S, Salvadeo A. Uremic pruritus is not related to plasma histamine concentrations. Clin Exp Dermatol 1995; 20: 294–296.

141. Francos GC, Kauh YC, Gittlen SD, Schulman ES, Besarab A, Goyal S, Burke JF. Elevated plasma histamine in chronic uremia. Effects of ketotifen. Int J Dermatol 1991; 30: 884–889.

142. Gill DS, Fonseca VA, Barradas MA, Balliod R, Moorhead JF, Dandona P. Plasma histamine in patients with chronic renal failure and nephrotic syndrome. J Clin Pathol 1991; 44: 243–245.

143. Poignet J, Callebert J, Delons S, Tabuteau F, Chaveau P, Bonete R, et al. Plasma histamine levels and kinetics in chronic hemodialysis patients. ASAIO Trans 1989; 35: 252–254.

144. Stockenhuber F, Kurz RW, Sertl K, Grimm G, Balcke P. Increased plasma histamine levels in uraemic pruritus. Clin Sci 1990; 79: 477–482.

145. DeMarchi S, Cecchin E, Villalta D, Sepiacci G, Santini G, Bartoli E. Relief of pruritus and decrease in plasma histamine concentrations during erythropoietin therapy in patients with uremia. N Engl J Med 1992; 326: 969–974.

146. Piazza V, DeFilippi C, Aprile C, Efficace E, Pisati P, Sacchi S, Salvadeo A. Uremic pruritus and plasma histamine concentration. Nephrol Dial Transplant 1993; 8: 670–671.

147. Weisshaar E, Dunker N, Domröse U, Neumann KH, Gollnick H. Plasma serotonin and histamine levels in hemodialysis-related pruritus are not significantly influenced by 5-HT3 receptor blocker and antihistaminic therapy. Clin Nephrol 2003; 59: 124–129.

148. Cho YL, Liu HN, Huang TP, Tarng DC. Uremic pruritus: roles of parathyroid hormone and substance P. J Am Acad Dermatol 1997; 36: 538–543.

149. Yosipovitch G, Reis J, Tur E, Sprecher E, Yarnitsky D, Boner G. Sweat secretion, stratum corneum hydration, small nerve function and pruritus in patients with advanced chronic renal failure. Br J Dermatol 1995; 133: 561–564.

150. Kato A, Hamada M, Maruyama T, Maruyama Y, Hishida A. Pruritus and hydration state of stratum corneum in hemodialysis patients. Am J Nephrol 2000; 20 437–442.

151. Kerr PG, Argiles A, Mion C. Whole blood serotonin levels are markedly elevated in patients on dialytic therapy. Am J Nephrol 1992; 12: 14–18.

152. Ashmore SD, Jones CH, Newstead CG, Daly MJ, Chrystin H. Ondansetron therapy for uremic patients in hemodialysis patients. Am J Kid Dis 2000; 35: 827–831.

153. Murphy M, Reaich D, Pai P, Finn P, Carmichael AJ. A randomised, placebo-controlled, double-blind trial of ondansetron in renal itch. Br J Dermatol 2003; 148: 314–317.

154. Mettang T, Pauli-Magnus C. The pathophysiological puzzle of uremic pruritus – insights and speculations from therapeutic and epidemiological studies. Perit Dial Int 2000; 20: 493–494.

155. Urbonas A, Schwartz RA, Szepietowski JC. Uremic pruritus – an update. Am J Nephrol 2001; 21: 343–350.

156. Pauli-Magnus C, Klumpp S, Alscher DM, Kuhlmann U, Mettang T. Short-term efficacy of tacrolimus ointment in severe uremic pruritus. Perit Dial Int 2000; 20: 802–803.

157. Balaskas EV, Bamihas GI, Karamouzis M, Voyiatzis G, Tourkantonis A. Histamine and serotonin in uremic pruritus: effect of ondansetron in CAPD-pruritic patients. Nephron 1998; 78: 395–402.

158. Silva SRB, Viana PCF, Lugon NV, Hoette M, Ruzany F, Lugon JR. Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. Nephron 1994; 67: 270–273.

159. Peer G, Kivity S, Agami O, Firemen E, Silverberg D, Blum M, Iaina A. Randomised cross-over trial of naltrexone in uremic pruritus. Lancet 1996; 348: 1552–1554.

160. Pauli-Magnus C, Mikus G, Alscher DM, Kirschner T, Nagel W, Gugeler N, et al. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. J Am Soc Nephrol 2000; 11: 514–519.

161. Breneman DC, Cardone JS, Blumsack RF, Lather RM, Searle EA, Pollack VE. Topical capsaicin for treatment of hemodialysis-related pruritus. J Am Acad Dermatol 1992; 26: 91–94.

162. Tarng DC, Cho YL, Liu HN, Huang TP. Hemodialysis-related pruritus. A double-blind, placebo-controlled, crossover study of capsaicin 0.025% cream. Nephron 1996; 72: 617–622.

163. Masi CM, Cohen EP. Dialysis efficacy and itching in renal failure. Nephron 1992; 62: 257–261.

164. Cacoub P, Poynard T, Ghillan P, Charlotte P, Olivi M, Piette JC, Opolon P for the Multivirc Group. Extrahepatic manifestations of chronic hepatitis C. Arthritis Rheum 1999; 42: 2204–2212.

165. Cribier B, Samain F, Vetter D, Heid E, Crosshans E. Systematic cutaneous examination in hepatitis C virus infected patients. Acta Derm Venereol 1998; 78: 355–357.

166. Cribier B, Santinelli F, Schmitt C, Stoll-Keller F, Grosshans E. Should patients with pruritus be tested for hepatitis C virus infection? A case-controlled study. Br J Dermatol 2000; 142: 1234–1235.

167. Nunes ACR, Amaro P, Maçôas F, Cipriano A, Martins I, Rosa A, et al. Fosinopril-induced prolonged cholestatic jaundice and pruritus: a first case report. Eur J Gastroenterol Hepatol 2001; 13: 279–282.

168. Ryatt KS, Cotteril JA, Littlewood JM. Generalized pruritus in a baby as a presenting feature of the arteriohepatic dysplasia syndrome. Clin Exp Dermatol 1983; 8: 657–661.

169. Jones EA, Bergasa NV. Evolving concepts of the pathogenesis and treatment of the pruritus of cholestasis. Can J Gastroenterol 2000; 14: 33–39.

170. Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. Lancet 1999; 355: 657–658.

171. Prince MI, Burt AD, Jones DEJ. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. Gut 2002; 50: 436–439.

172. Berg CI. Use of colesevalem hydrochloride (Welchtol) as a novel therapeutic agent for the management of refractory pruritus in chronic liver disease. Hepatology 2001; 34: 541.

173. Wolfhagen FHJ, Sternieri E, Hop WCJ, Vitale G, Bertolotti M, van Buuren HR. Oral naltrexone treatment for cholestatic pruritus: A double-blind placebo-controlled study. Gastroenterology 1997; 113: 1264–1269.

174. Terg R, Coronel E, Sordá J, Munoz AE, Findor J. Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. J Hepatol 2002: 37: 717–722.

175. Lewiecki MEM, Rahman F. Pruritus: A manifestation of iron deficiency. JAMA 1976; 236: 2319–2320.

176. Valsecchi R, Cainelli T. Generalized pruritus: A manifestation of iron deficiency. Arch Dermatol 1983; 119: 630.

177. Diehn F, Tefferi A. Pruritus in polycythemia vera: prevalence, laboratory correlates and management. Br J Haematol 2001; 115: 619–621.

178. Tefferi A, Fonseca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. Blood 2002; 99: 2627.

179. Zylicz Z, Krajnik M. Pruritus in cancer: uncommon, but sometimes worse than pain. Ned Tijdschr Geneeskd 1999; 143: 1937–1940.

180. Stefanato CM, Reyes-Mugica M. Masked Hodgkin's disease: The pruriginous disguise. Ped Hematol Oncol 1996; 13: 293–294.

181. Feiner AS, Mahmood T, Wallner S. Prognostic importance of pruritus in Hodgkin's disease. JAMA 1978; 240: 2738–2740.

182. Neilly JB, Martin A, Simpson N, Maccuisk AC. Pruritus in diabetes mellitus: Investigation of prevalence and correlation with diabetes control. Diabetes Care 1986; 9: 273–275.

183. Leylek OA, Unlü S, Oztürkcan S, Cetin A, Sahin M, Yildiz E. Estrogen dermatitis. Eur J Obstr Gynecol 1997; 72: 97–103.

184. Bugalho MJGM, Limbert E, Sobrinho LG, Clode AL, Soares J, Nunes JFM, Conceição Pereira M. A kindred with multiple endocrine neoplasia type 2A associated with pruritic skin lesions. Cancer 1992; 70: 2664–2667.

185. Gelfand JM, Rudikoff D. Evaluation and treatment of itching in HIV-infected patients. Mount Sinai J Med 2001; 68: 298–308.

186. Berger TG, Dhar A. Lichenoid photoeruptions in human immunodeficiency virus infection. Arch Dermatol 1994; 130: 618–623.

187. Milazzo F, Piconi S, Trabattoni D, Magni C, Capetti A, Fusi ML, et al. Intractable pruritus in HIV infection: immunologic characterization. Allergy 2000; 54: 266–272.

188. Lim HW, Vallurupalli S, Meola T, Soter NA. UVB phototherapy is an effective treatment for pruritus in patients infected with HIV. J Am Acad Dermatol 1997; 37: 414–417.

189. Gelfand JM, Rudikoff D, Lebwohl M, Klotman ME. Effect of UV-B phototherapy on plasma HIV type 1 RNA viral level: A self-controlled prospective study. Arch Dermatol 1998; 134: 940–945.

190. Berman B, Flores F, Burke G. Efficacy of pentoxifylline in the treatment of pruritic papular eruption of HIV-infected persons. J Am Acad Dermatol 1998; 38: 955–959.

191. Smith KJ, Skelton HG, Yeager J. Pruritus in HIV 1 disease: Therapy with drugs which may modulate the pattern of immune dysregulation. Dermatology 1997; 195: 353–358.

192. Radomsky LL, Levine N. Thalidomide. Derm Clin 2001; 19: 87–103.

193. Calabrese L, Fleischer AB Jr. Thalidomide: current and potential clinical applications. Am J Med 2000; 108: 487–495.

194. Holmes RC. Polymorphic eruption in pregnancy. Sem Dermatol 1989; 8: 18–22.

195. Aronson IK, Bond S, Fiedler VC, Vomvouras S, Gruber D, Ruiz C. Pruritic urticarial papules and plaques of pregnancy: Clinical and immunopathologic observations in 57 patients. J Am Acad Dermatol 1998; 39: 933–939.

196. Lunzer MR. Jaundice in pregnancy. Baillières Clin Gastroenterol 1989; 3: 467–483.

197. Clark TJ, Dwarakanath L, Weaver JB. Pruritus in pregnancy and obstetric cholestasis. Hospital Medicine 1999; 60: 254–260.

198. Riikonen S, Savonius H, Gylling H, Nikkila K, Tuomi AM, Miettinen TA. Oral guar gum, a gel-forming dietary fiber relieves pruritus in intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand 2000; 79: 260–264.

199. Kaplan AP. Drug-induced skin disease. J Allergy Clin Immunol 1984; 74: 573–579.

200. Metze D, Reimann S, Szepfalusi Z, Bohle B, Kraft D, Luger T. Persistent pruritus after hydroxyethyl starch infusion therapy: a result of a long-term storage in cutaneous nerves. Br J Dermatol 1997; 136: 553–559.

201. Ständer S, Bone HG, Machens HG, Aberle T, Burchard W, Prien T, et al. Hydroxyethyl starch does not cross the blood-brain or the placental barrier but the perineurium of peripheral nerves in infused animals. Cell Tissue Res 2002; 310: 279–287.

202. Sirtl C, Laubenthal H, Zumtobel V, Kraft D, Jurecka W. Tissue deposits of hydroxyethyl starch (HES): dose-dependent and time related. Br J Anaest 1999; 82: 510–515.

203. Szeimies RM, Stolz W, Wlotzke U, Korting HC, Landthaler M. Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. Br J Dermatol 1994; 131: 380–382.

204. Koo J, Gambla C. Delusions of parasitosis and other forms of monosymptomatic hypochondriasis. Dermatol Clin 1996; 14: 429–438.

205. Biondi M, Arcangeli T, Petrucci RM. Paroxetine in a case of psychogenic pruritus and neurotic excoriations. Psychother Psychosom 2000; 69:165–166.

206. Fisher DA. Brachioradial pruritus: A recurrent solar dermopathy. JAAD 1999; 41: 656–657.

207. Wallengren J. Brachioradial pruritus: A recurrent solar dermopathy. J Am Acad Dermatol 1998; 39: 803–806.

208. Kavak A, Dosoglu M. Can a spinal tumor cause brachioradial pruritus? J Am Acad Dermatol 2002; 46: 437–440.

209. Wallengren J, Sundler F. Cutaneous field stimulation in the treatment of severe itch. Arch Dermatol 2001; 137: 1323–1325.

210. Astwazaturow M. Über paresthetische Neuralgien und eine besondere Form derselben – Nothalgia paresthetica. Nervenarzt (Berlin) 1934; 133: 88.

211. Savk E, Savk Ö, Bolukbasi O, Culhaci N, Dikicioglu E, Karaman G, Sendur N. Notalgia paresthetica: a study on pathogenesis. Int J Dermatol 2000; 39: 754–759.

212. Wallengren J, Klinher M. Successful treatment of notalgia paresthetica with topical capsaicin: vehicle-controlled, double-blind, cross-over study. J Am Acad Dermatol 1995; 32: 287–289.

213. Goulden V, Toomey PJ, Highet AS. Successful treatment of notalgia paresthetica with a paravertebral local anesthetic block. J Am Acad Dermatol 1998; 38: 114–116.

214. Drake LA, Fallon JD, Sober A. The Doxepin Study Group. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. J Am Acad Dermatol 1994; 31: 613–616.

215. Drake LA, Milikan LE. The Doxepin Study Group. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Arch Dermatol 1995; 131: 1403–1408.

216. Taylor JS, Praditsuwan P, Handel D, Kuffner G. Allergic contact dermatitis from doxepin cream. One-year patch test clinical experience. Arch Dermatol 1996; 132: 515–18.

217. Nolano M, Simone DA, Wendelschaffer-Crabb G, Johnson T, Hazen E, Kennedy WR. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. Pain 1999; 81: 135–145.

218. Skaehill PA. Tacrolimus in dermatological disorders. Ann Pharmacother 2001; 35: 582–587.
219. Daly M, Shuster S. Effect of aspirin on pruritus. BMJ 1986; 293: 907.
220. Hägermark Ö. Influence of antihistamines, sedatives, and aspirin on experimental itch. Acta Derm Venereol 1973; 53: 363–368.
221. Yosipovitch G, Sugeng MW, Chan YH, Goon A, Ngim S, Goh CL. The effect of topically applied aspirin on localized circumscribed neurodermatitis. J Am Acad Dermatol 2001; 45: 910–913.
222. Zhai H, Hannon W, Hahn GS, Harper RA, Pelosi A, Maibach HI. Strontium nitrate decreased histamine-induced itch magnitude and duration in man. Dermatology 2000; 200: 244–246.
223. Miller MJS, Vergnolle N, McKnight W, Musah RA, Davison CA, Trentacosti AM, et al. Inhibition of neurogenic inflammation by the Amazonian herbal medicine Sangre de Grado. J Invest Dermatol 2001; 117: 725–730.
224. Epstein E, Pinkus JB. A blind study. Arch Dermatol 1964; 89: 548–549.
225. Tennyson H, Levine N. Neurotropic and psychotropic drugs in dermatology. Derm Clin 2001; 19: 179–197.
226. Schwörer H, Hartmann H, Ramadori G. Relief of cholestatic pruritus by a novel class of drugs: 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists: effectiveness of ondansetron. Pain 1995; 61: 33–37.
227. Larijani GE, Golberg ME, Roger KH. Treatment of opioid-induced pruritus with ondansetron: report of four patients. Pharmacotherapy 1996; 16: 958–960.
228. Kjellberg F, Tamer MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. Eur J Anaest 2001; 18: 246–257.
229. Beckwitt Turkel S, Nadala JGB, Wincor MZ. Possible serotonin syndrome in association with 5-HT (3) receptor antagonist agent. Psychosomatics 2001; 42: 258–260.
230. Nilsson HJ, Levinsson A, Schouenborg J. Cutaneous field stimulation (CFS): a new powerful method to combat itch. Pain 1997; 71: 49–55.
231. Wallengren J. Cutaneous field stimulation of sensory nerve fibers reduces itch without affecting contact dermatitis. Allergy 2002: 57: 1195–1199.
232. Belgrade MJ, Solomon LM, Lichter EA. Effect of acupuncture on experimentally induced itch. Acta Derm Venereol 1984; 64: 129–133.
233. Ghent CN, Carruther SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. Gastroenterol 1988; 94: 488–493.
234. Bergasa NV, Alling DW, Talbot TC, Swain MG, Yurdaydin C, Turner MC, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. Am Intern Med 1995; 123: 161–167.
235. Bergasa NV, Alling DW, Talbot TL, Wells MC, Jones EA. Oral nalmefene therapy reduces scratching activity due to the pruritus of cholestasis: A controlled study. J Am Acad Dermatol 1999; 41: 431–434.
236. Borgeat A, Wilder-Smith O, Mentha G, Huber O. Propofol and cholestatic pruritus. Am J Gastroenterol 1992; 87: 672–674.
237. McCormick PA, Scott F, Epstein O, Burroughs AK, Scheuer PJ, McIntyre N. Thalidomide as therapy for primary biliary cirrhosis: a double-blind placebo-controlled pilot study. J Hepatol 1994; 21: 496–499.
238. Müller C, Pongratz S, Ridlich J, Penner E, Kaider A, Schemper M, et al. Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron. Eur J Gastroenterol Hepatol 1998; 10: 865–870.
239. O'Donohue JW, Haigh C, Williams R. Ondansetron in the treatment of the pruritus of cholestasis: a randomized controlled trial. Gastroenterol 1997; 112: A 1349.
240. Raiford DS. Pruritus of chronic cholestasis. Q J Med 1995; 88: 603–607.
241. Walt RP. Effect of stanozolol on itching in primary biliary cirrhosis. BMJ 1988; 296: 607.
242. Bergasa NV, Link MJ, Keogh M, Yarosloavsky G, Rosenthal RN, McGee M. Pilot study of bright-light therapy reflected toward the eyes for the pruritus of chronic liver disease. Am J Gastroenterol 2001; 96: 1563–1570.
243. Watson CPN, Tyler KL, Bichers SDR, Milikan LE, Smith S, Coleman E. A randomized, vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. Clin Ther 1993; 15: 510–526.
244. The Capsaicin Study Group. Treatment of painful diabetic neuro-pathy with topical capsaicin. Arch Intern Med 1991; 151: 2225–2229.
245. Watson CPN, Evans RJ. The postmastectomy pain syndrome and topical capsaicin: a randomised trial. Pain 1992; 51: 375–379.
246. Bernstein JE, Parish LC, Rapaport M, Rosenbaum MM, Roenigk HH. Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. J Am Acad Dermatol 1986; 15: 504–507.
247. Ellis CN, Berberian B, Sulica VI, Dodd WA, Jarratt MT, Katz I. A double-blind evaluation of topical capsaicin in pruritic psoriasis. J Am Acad Dermatol 1993; 29: 438–442.
248. Jancso G, Lynn B. Possible use of capsaicin in pain therapy. Clin J Pain 1987; 3: 123–126.
249. Reimann S, Luger T, Metze D. Topical capsaicin for the treatment of itch and pain in dermatological patients. Hautarzt 2000; 51: 164–172.
250. Tupker RA, Coenrad PJ, van der Meer JB. Treatment of prurigo nodularis, chronic prurigo and neurodermitis circumscripta with topical capsaicin. Acta Derm Venereol 1992; 72: 463–465.
251. Marks JG. Treatment of apocrine chromhidrosis with topical capsaicin. J Am Acad Dermatol 1989; 21: 418–420.
252. Kirby B, Rogers S. Treatment of PUVA itch with capsaicin. Br J Dermatol 1997; 137: 152.
253. Neess CM, Hinrichs R, Dissemond J, Herrmann G, Poswig A, Servera-Llanras M, et al. Treatment of pruritus by capsaicin in a patient with pityriasis rubra pilaris receiving Re-PUVA therapy. Clin Exp Dermatol 2000; 25: 209–211.
254. Williams LC, Nesbitt LT. Update on systemic glucocorticosteroids in dermatology. Dermatol Clin 2001; 19: 63–77.
255. Cather JC, Abramovits W, Menter A. Cyclosporine and tacrolimus in dermatology. Dermatol Clin 2001; 19: 119–137.
256. Daly M, Shuster S. Antipruritic action of thalidomide. Acta Derm Venereol 2000; 80: 24–25.
257. Kjellberg F, Tramer MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. Eur J Anaesth 2001; 18: 346–357.
258. Zylic Z, Smith S, Krajnik M. Paroxetine for pruritus in advanced cancer. J Pain Symptom Manag 1998; 16: 121–124.