Pruritus: A New Look at an Old Problem

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Pruritus, a frequent complaint heard by family physicians, is a complex physiological phenomenon mediated by histamine and other peptides. It is associated with a number of common dermatologic diseases but has significant psychological factors as well. In some patients pruritus may be an important marker of systemic disease. Diagnostic approach includes a careful physical examination of primary skin lesions and goal-directed laboratory tests. Careful skin care and oral antihistamines are basic measures to alleviate pruritus.

Pruritus, or itching, is a frequent complaint heard by family physicians. Although generally considered to be a benign symptom, pruritis can have adverse affects on patients' well-being and can be incapacitating in its severe form. The mechanisms of pruritus are not particularly well understood and are compounded by the subjective nature of the process itself. Pruritus occurs with a host of dermatologic conditions but can also be a marker of systemic disease. It is clearly important for the family physician to be aware of the varied causes of itching.

Everyone knows what the sensation of itch is, yet it is an elusive concept to define. The term *itch* is commonly used in the English language—we itch to get our hands on something, we scratch our heads to solve a problem, and who among us does not have the itch to succeed? Itching has been defined by Tonneson[1] as "an irritating sensation which evokes the impulse to scratch." The aggravating and nonadapting nature that invokes scratching distinguishes itching from other cutaneous sensations, such as pain, touch, and temperature.

Physiologically, itching is the conscious expression of cutaneous sensations that evoke the well-known scratch reflex. The purpose of this reflex is the removal of the noxious stimulus. Unfortunately scratching can cause further damage to the skin and can perpetuate the problem. Severe pruritus can be relieved by self-trauma, essentially replacing itching with pain, but such action can result in chronic skin changes of lichenification, erythema, excoriation, and even lacerations.

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PATHOPHYSIOLOGY

The actual sensation of itching is believed to be produced by stimulation of the small, slow C and possibly A delta fibers in the superficial layers of the skin. These are nonmyelinated, polymodal fibers, each having varying threshholds. None are uniquely adapted to itch; indeed, pain, touch, and pressure can be registered centrally by these fibers.

Itching is distinct from pain but related; it is sometimes called mild pain. Both electrical and thermal stimulations can cause itch, then pain.[2] When anesthesia is induced by vascular occlusion, both pain and itch disappear. In paraplegic patients, when pain is absent, itch is also absent. That C fibers carry both sensations explains the overlap, yet the body senses can clearly distinguish between the two.

Histologic evidence has shown repetitive scratching can cause loss of nerve fibers. Theoretically a selective loss of the larger fibers can upset the balance of incoming stimuli, leaving itch stimuli unopposed and magnified. The old adage, "scratching makes it worse," may have a real pathophysiological basis.

Mediators

There are a number of mediators of the itch response. The first recognized, and probably most important, is histamine. Pricking the skin with a 1:100,000 dilution of histamine will produce pruritus in most individuals and can be used to determine specific thresholds.[3] Histamine found in the granules of dermal mast cells as well as in some epidermal cells is believed to act directly on nerve endings, perhaps by potentiating the response of neurons to depolarizing agents, which act through cyclic adenosine

TABLE 1. DERMATOLOGIC CAUSES OF PRURITUS

Xerosis
Atopic dermatitis
Scabies
Dermatitis herpetiformis
Lichen simplex chronicus
Psoriasis
Lichen palnus
Contact dermatitis
Fungal infections
Insect bites
Pediculosis
Urticaria
Sunburn
Polymorphous light eruption
Pityriasis rosea
Electrostatic charges (nylon and wool friction)
Plaster of Paris casts
Fiberglass—other irritants

monophosphate (AMP).[4] Most of the evidence is indirect; indeed, one can have itch without the other histamine-mediated effects (eg, erythema or vasodilation). Furthermore, antihistamines can control such histamine-mediated responses as urticaria without affecting itch, so clearly histamine is not the only mediator.

Other mediators of the itch response have been appreciated historically. Mucuna pruriens, a tropical plant whose pods are covered by cowhage spicules, is known to cause ferocious itching. Although this plant was first described by an English physician who accompanied the Duke of Albermarle on a trip to Jamaica in 1688, the natives knew about it for some time.[4] The natives would eat this inhospitable bean in times of scarcity only. They would heat the spicules to prevent the itching, for it was felt for some time that the spicules themselves caused the itching. In fact, the name cowhage is from the Hindu *kiwach,* or bad rubbing. In the late 18th century, William Chamberlain sprinkled cowhage on intestinal roundworms and noted their hyperactivity (itching?), causing them to release their hold on the intestinal mucosa. He noted that prior boiling of the spicules eliminated this effect, and the worms stayed happily attached to the intestine.

It was not until 1955 that Shelley and Arthur[5] isolated a heat-labile endopeptidase from the mucuna plant, mucunain, which produces itching upon subepidermal injection. Thus, the Jamaicans were unknowingly altering a heat-labile substance when they boiled the spicules of the mucuna plant!

Subsequently, many other peptidases have been shown to be produced by epidermal or dermal cells from inflammation and give rise to itching. A number of peptides are also known to cause a vascular response and varying degrees of itch, including kinins, vasoactive intestinal protein, enkephalin, and substance P. The effects of these substances may be mediated through the subsequent release of histamine, since exhaustion of skin histamine by agent 48:80 (a histamine releasor) or H_1 blockers can prevent these responses.

Other possible mediators of the itch response include platelet-derived serotonin, prostaglandins, and leukotrienes. Mechanical factors may play a role including heat (vasodilation) and xerosis. Nighttime pruritus, which is often organic in nature, is associated with increased parasympathetic activity and a lowered threshold to itching.

ETIOLOGY

Dermatological

When approaching the itching patient, one should first consider a variety of skin diseases that are known to cause pruritus (Table 1). Xerosis, or dry skin, by itself is a cause of significant pruritus. A particularly common problem in the elderly, xerosis may be exacerbated by environmental factors such as cold air, low humidity, or central heating. Atopic dermatitis, or eczema, is a chronic skin disorder usually presenting in infancy or childhood. Involved areas, such as the flexor surfaces, will be quite pruritic, and papules may appear with varying degrees of lichenification depending upon the amount of scratching. A personal or family history of atopy (eczema, asthma, or hayfever) is helpful in identifying this condition.

A common, easily missed, and treatable condition is scabies, a fiercely pruritic disorder caused by the mite Sarcoptes scabiei. Patients with these parasites can have itching over their entire body without primary skin lesions but will usually have widespread excoriations. A history of scabies and other family members with similar problems is suggestive of this condition, and infants may be affected as well. The diagnosis is made by identification of the mite from skin scrapings, and treatment involves overnight application of lindane or other antiscabetic preparations.

Dermatitis herpetiformis is an uncommon, but intensely pruritic, papulovesicular eruption occurring on extensor surfaces in young adults. The diagnosis is made on clinical and histological evidence.

Lichen simplex chronicus, or neurodermatitis, refers to localized, lichenified patches of pruritic skin caused by frequent scratching. The stimulus for itching is unknown, but these areas may respond to local application of corticosteroids.

A host of other dermatologic conditions may cause pruritus. A careful history and physical examination can

aid in the diagnosis of many of these disorders. Some have characteristic clinical findings, such as the silver erythematous scales of psoriasis, the linear vesicular eruptions of contact dermatitis, and the flat-topped violaceous papules of lichen planus. Urticaria will usually exhibit raised blanching wheals, and pityriasis rosea classically exhibits a "herald patch" followed by a scaling truncal rash in a fir tree distribution. Fiberglass is a rare but important skin irritant. Patients place fiberglass curtains in a washing machine; their clothes subsequently become impregnated with the fibers, causing a severe and vexing pruritus.

Psychological

Pruritus, like pain, is not simply a physiologic expression; it has a profound psychological component. No two people react to itching in the same manner. Many factors come into play, including the state of consciousness, attentiveness, and the ability to relieve the sensation by scratching.

Patients with persistent pruritus and no specific diagnosis are often found to be outwardly calm, but hiding feelings of hurt, anger, weakness, and inferiority.[6] These patients may wear their emotions on their skin rather than on their sleeve. Other studies show scratching to represent pent-up resentment or a form of self-punishment.[7] Musaph,[8] after examining hundreds of patients with pruritus of uncertain etiology, feels that itching is a result of thwarted emotion. Many patients scratch without itching as a release of emotional tension. Furthermore, since scratching can produce mild pain, pleasure, and afterglow, Musaph likens the itch-scratch pleasure cycle to a form of autoeroticism. In other patients, it may be a form of torture and self-punishment.

It is clear that tensions and repressed emotions are involved in the itching patient. As physicians, it is important to make some attempt to sort out the role these factors play. Telling a patient that the itching is "in his head" will not solve the problem and may create further adverse feelings. The patient should be reassuringly educated to the various roles that emotions may play. Serious underlying conflicts, when present, must be evaluated and treated.

Systemic

The patient with generalized pruritus who presents without obvious dermatological or psychological cause should be evaluated for systemic disease (Table 2).

Chronic renal failure is an important cause of persistent generalized pruritus. Uremic patients, who now live longer since the advent of dialysis, have an increased incidence of pruritus.[9]

TABLE 2. SYSTEMIC DISEASES ASSOCIATED WITH PRURITUS

Chronic renal failure
Hepatic cholestasis
Primary biliary cirrhosis
Cholestasis of pregnancy
Oral contraceptives
Extrahepatic biliary obstruction
Hepatitis
Drugs
Hematopoietic
Polycythemia vera
Hodgkin's disease
Multiple myeloma
Mastocytosis
Iron deficiency anemia
Endocrine
Thyrotoxicosis
Hypothyroid
Carcinoid
Miscellaneous
Asthma
Atypical angina
Tumors
Opiates and other drugs
Foods (bananas, coffee)

Fifty years ago, 20 percent of patients with uremia developed pruritus, now 80 to 90 percent may eventually develop severe intractable itching. The pruritus may occur anywhere on the body, is not associated with skin lesions, and is only loosely correlated with the degree of uremia. The cause is uncertain, but theories include elevated histamine levels, secondary hyperparathyroidism, and peripheral neuropathy. The ineffectiveness of H_1 and H_2 blockers implicates an endopeptidase or kinin, which may accumulate. Successful clinical trials with ultraviolet light suggest a photolabile systemic mediator.[10]

Hepatic cholestasis can cause pruritus in a variety of diseases. Nearly all patients with primary biliary cirrhosis have pruritis, and it can be the presenting manifestation in up to one half of all cases. Cholestasis of pregnancy, extraheptic biliary obstruction, hepatitis, and a number of drugs, including phenothiazines, tolbutamide, erythromycin, and oral contraceptives, can all cause significant pruritus. The itching may be related to an accumulation of bile salts in the skin, although there is no direct correlation. The bile salts may directly affect cutaneous nerves, causing mast cells to release histamine, or may liberate proteases, which subsequently cause pruritus.[11]

A number of unrelated hematopoietic diseases are associated with pruritus. Patients with polycythemia vera will frequently have pruritus that is aggravated by hot

baths. Fifty percent of patients with Hodgkin's disease may have pruritus, and in one study, pruritus was considered to be a bad prognostic sign compared with stage-matched patients without pruritus.[12] Multiple myeloma, mastocytosis, and iron deficiency anemia may also present with itching.

Among the endocrine diseases, thyrotoxicosis is associated with itching in up to 10 percent of patients, especially those with longstanding disease. The increased body temperature, kinins, and vasodilation all play a role. Hypothyroidism probably contributes to pruritus through the associated dry skin. Diabetes is a frequently quoted but poorly documented cause of generalized pruritus. The best documented study only had an incidence of 3 percent, indicating some overestimation.[13] Diabetics are prone, however, to pruritus ani and vulvae from candidal infections. Carcinoid syndrome, though rare, can be the cause of pruritus associated with increased histamine and kallikrein levels.

Through a degranulation of mast cells, the opiates may cause pruritus, which may be the presenting complaint of drug addicts. There are case reports of asthma presenting with prodromol itching,[14] atypical angina associated with nasal pruritus,[15] and brain tumors manifesting with ferocious itching of the nostrils.[16]

DIAGNOSTIC APPROACH

When evaluating the patient with significant pruritus, the physician should obtain a careful history, paying attention to the severity and quality of the itching and the influence of environmental factors. Some attempt must be made to assess the patient's overall psychological state and the degree of disruption of his or her lifestyle. During physical examinations careful note should be made of primary skin lesions, which may suggest a dermatologic diagnosis, as well as secondary lesions from scratching. Persistent rubbing can cause erythema and eventually confluent plaques of lichenified skin, which are indistinguishable from atopic dermatitis. Prolonged scratching can cause the free margin of the nails to become beveled and may aid in the diagnosis when patients are unaware of their scratching.

For those patients without overt causes or primary skin lesions, a limited laboratory workup is recommended. A complete blood count is an effective screening procedure for hematopoietic disorders. Liver function tests are indicated to rule out cholestatic disorders, and blood urea nitrogen, creatinine, and urinalysis tests will detect serious renal disease. A chest roentgenogram will show overt mediastinal enlargement associated with Hodgkin's disease. A thyroid screening test is probably indicated, although it will have a low yield in the absence of suggestive factors and can be considered optional.

TREATMENT

The treatment of pruritus is often an unsatisfactory endeavor for both the patient and the physician. The number of different causes suggests that the treatment will be quite varied. Difficulty in treatment is further compounded by the subjective nature of the complaint. In a simple but elegant study, Epstein and Pinski[17] treated patients suffering from pruritic dermatoses with four different tablets. Two thirds of the patients benefited from at least one of the preparations, though all four tablets were placebo!

If a dermatologic disease can be identified, specific treatment can be offered. Antihistamines are the mainstay of treatment for pruritus. They may act only by sedation and are clearly ineffective in some patients, yet histamine is the most consistent mediator, and these agents should always be tried. Hydroxyzine is the most widely used agent, and adult doses may range from 30 mg/d in the elderly to 100 mg/d and even 200 mg/d in adults. The dose response is individualistic and should be titrated by consideration of sedation or other central nervous system effects. It is better to give the drug on a regular schedule rather than intermittently, similar to pain control. If one class of antihistamines is ineffective at an adequate dose, another class should be tried; two different classes given together occasionally give added benefit. H_2 blockers, such as cimetidine, have not been shown to be effective.

The skin, as a rule, should be kept moisturized with bland emollients, such as petrolatum jelly, several times a day. Patients are advised to use a bath oil, and if showering, to avoid very hot water. All soaps can be drying, and superfatted soaps such as Dove or Basis are helpful in preventing further xerosis. Moisturizers should be applied within minutes after drying from a shower or bath so as to "seal in" the hydrated skin. Topical application of 0.5 percent menthol provides a soothing effect, but topical anesthetics may sensitize the patient and should be avoided.

Many physical modalities have been tried for pruritus and are the basis for some folk remedies. Pain may replace itch when placing the itching area under scalding hot water. Although effective, the subsequent vasodilation and edema can cause a rebound itch, and cold water is preferred.

Pinpricks near or in the same dermatome can abolish the itch sensation; this effect is the basis of relief by scratching.[18] Unfortunately, repeated scratching can cause extensive damage to the skin and may alter nerve fibers, leading to a worsening of the condition.

There has been renewed interest in central nervous system agents such as naloxone, an opiate antagonist that has been shown to relieve intractable pruritus in some cases.[19] The opiate like enkephalins may play a role here as well as in the placebo response. Antidepressants, such

as doxepin, have antihistaminic and antipruritic effects and may be useful in psychogenic pruritus.

A recent advance is the use of ultraviolet B light for uremic pruritus, with excellent and lasting results.[10] The mechanism, though uncertain, may involve the phototherapeutic inactivation of a circulating substance present in uremia. Cholestyramine, an oral anion exchange resin, is clearly effective for the relief of biliary pruritus. The mechanism is also uncertain, but may be partially related to the removal of bile salts.[11]

CONCLUSIONS

In summary, pruritus is a complex, yet not uncommon, phenomenon of great interest to family physicians. There is no single mediator of this sensation, and much needs to be learned. Through a careful history and physical examination, the physician may be able to separate the causes into dermatologic, psychologic, or systemic. Specific treatments can be undertaken where appropriate, and general measures, such as antihistamines and emollients, can also provide significant benefit.

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