6 Water-Induced Pruritus

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Water is one of the most ubiquitous and trusted substance on earth and one that we contact daily in a myriad of ways. Indeed, our very bodies are composed primarily of this essential compound. We expect that our routine contacts with water will be at worst harmless and at best beneficial and pleasurable. Therefore, it is difficult to imagine that there are those who experience severe itching simply from exposure to water. The purpose of this review is to discuss those conditions that may manifest pruritus on contact with water and to describe in detail those in which water contact per se incites extreme discomfort. These later conditions include aquagenic pruritus (AP), polycythemia rubra vera (PRV), and aquagenic pruritus of the elderly (APE).

Mild, transient itching following water contact is not uncommon, and its existence probably goes unreported by most patients. For instance, patients with eczema or asteatosis may note itching following bathing. This pruritus is usually mild and transient, varies with the severity of the skin disease, commonly occurs unassociated with water contact, and does not consistently occur with water contact. Severe pruritus that is consistently associated either with all forms of water contact or with only specific forms is uncommon.

Logan et al.[1] questioned 363 consecutive new dermatology outpatients regarding any history of pruritus associated with water contact. They questioned 182 male and 181 female patients, ranging in age from 3–75 years of age; 137 (37.7%) reported having experienced itching upon contact with water. In none of the 137 was water-related itching the presenting or secondary dermatologic complaint, and none was found to consistently experience pruritus upon water contact. Ninety-five of the 137 (69%) had a pruritic dermatosis such as eczema or asteatosis that could have accounted for the pruritus.

For the remaining individuals who complain of pruritus on water contact it is not the water but an associated factor that accounts for the discomfort. This is especially true for patients with one of the physical urticarias. Patients with cholinergic or heat urticaria may complain of wheals and pruritus on taking a hot bath or shower, but it is the warm temperature, not the water, that is responsible. Likewise, in cold urticaria, cold water contact may induce pruritic wheals, but the water per se is not the incitant. In patients with vibratory urticaria or symptomatic dermographism (SD), the jet of water from a shower nozzle may generate sufficient mechanical force to stimulate pruritus. Moreover,

patients with SD may complain of pruritus following all forms of water contact, but it is the toweling of the skin after bathing, not the water contact, that is responsible; hot conditions, such as in a warm bath, may also make the pruritus of SD worse.[2] This may pose some diagnostic difficulty, as the toweling may result in significant pruritus without producing easily observable lesions of dermographism. As will be discussed, these symptoms may thus mimic those of AP and PRV. Aquagenic urticaria (AU), one of the least common forms of physical urticaria, is one condition in which water contact per se, via an unknown pathway, does induce wheals and pruritus. AU is discussed in detail in chapter 7.

Patients complaining of water-induced pruritus (WIP) from one of the physical urticarias or SD manifest both wheals and itching, either after casual contact with water or on provocative testing. On the other hand, AP and PRV characteristically manifest severe pruritus without observable skin changes.

Thus, in evaluating a patient with WIP, one must consider several possible causes (Table 1). First, it is necessary to determine whether the discomfort is restricted to areas of dermatitis or xerosis; then, if the patient is elderly with severe asteatosis, APE may be considered. One must then exclude the physical urticarias and SD by clinical history and by performing appropriate provocative tests; these tests are well reviewed elsewhere.[3,4] Patients whose pruritus is not associated with cutaneous changes and is not localized to areas of dermatitis or xerosis should be further evaluated for the presence of AP or PRV.

TABLE 1. Common Causes of Water-Induced Itching

Xerosis or eczema
Aquagenic urticaria
Cholinergic urticaria
Cold urticaria
Heat urticaria
Vibratory urticaria
Symptomatic dermographism
Aquagenic pruritus
Polycythemia rubra vera
Aquagenic pruritus of the elderly

Aquagenic Pruritus

The term "aquagenic pruritus" was first used by Shelley in 1970[5] in discussing a case submitted to the Questions and Answers Section of the *Journal of the American Medical Association*. Although the etymologic validity of "aquagenic pruritus" has been debated (some have suggested aquagenous pruritus or hydrogenous pruritus), subsequent published reports of this condition have used the term "aquagenic pruritus," and it is, at least for now, the term of choice.

Greaves et al.[6] reported the first three fully documented cases of AP in 1981. Lotti,[8] Haustein,[9] Lubach,[10] and Bayoumi and Highet[11] have since reported a total of eight additional cases. From these cases and an additional 33 reported by Steinman and Greaves in 1985,[7] six criteria for the diagnosis of AP may be defined. These are summarized in Table 2.

AP is a fairly distinct, albeit poorly understood, clinical entity. It is slightly more common in males and can begin at any age. Nineteen females and 25 males have been reported, a ratio of 1:1.3. The age at onset varied from 8–78, with a mean of 42.6 years,[7] with no significant differences between age of onset in males and females. Haustein's patients were 42, 22, and 24.[9] Lubach's patients were 41 and 44 years old[10]; and Bayoumi and Highet's patients were 40 and 45[11] at the onset of their symptoms. The duration of symptoms prior to presentation ranged from 5 months–30 years. There have been no reports of complete remis-

TABLE 2. Criteria for the Diagnosis of Aquagenic Pruritus

1. Severe pruritus, prickling, stinging, or burning consistently develops after water contact, regardless of the water temperature.
2. The discomfort develops within minutes after water contact.
3. No visible skin changes occur.
4. No concurrent skin disease, internal disorder, or medication use can explain the discomfort.
5. Aquagenic, cholinergic, cold, heat, and vibratory urticaria, and symptomatic dermographism are excluded.
6. Polycythemia rubra vera is excluded.

sion of symptoms in any AP patient. Approximately 20% of the reported patients have had a personal or family history of atopy, a frequency no different from that of the general population. None has had concurrent atopic eczema, dermographism, or chronic idiopathic urticaria. Of the patients for whom published data are available, one third reported that one or more family members had symptoms consistent with a diagnosis of AP. With rare exceptions, all patients experienced pruritus on contact with water regardless of its temperature or salinity; two patients did not experience discomfort in cold salt water. In only two patients has there been a seasonal variability in the intensity of symptoms. These patients experienced more severe discomfort during the winter months.[10]

The kind of discomfort experienced by patients with AP is variable. For many, "pruritus" is not an appropriate name. Some describe their discomfort as itching, but many report prickling, stinging, or burning sensations. In approximately half, discomfort begins within 1–15 minutes after contact with water. In the rest, pruritus does not begin until 2–15 minutes after cessation of continuous water contact. The discomfort lasts from 10–120 minutes, usually about 40, and is usually severe. Many AP patients simply avoid tub or shower baths altogether and resort to regional sponge bathing only when necessary.

The distribution of the symptoms is variable. Individual patients characteristically experience pruritus only on specific skin areas. Application of water to affected areas can trigger local symptoms, while water contact circumscribed to other areas usually results in no discomfort. In Steinman and Greaves' 36 patients, the thighs and legs were affected in 35, the trunk in 26, and the shoulders or arms in 28. Symptoms began on the legs in 13 and were confined to the extremities in 9.[7] In almost all cases of AP, the head, palms, and soles are spared.[7,9,10]

Other stimuli incite the same symptoms in slightly more than half of the patients, but the discomfort is less consistent and severe. Of 36 patients questioned, perspiration (19/36), getting in or out of bed (18/36), changes in ambient temperature (17/36), heat (11/36), cold (9/36), physical exertion (7/36), emotional upset (7/36), and pressure (6/36) were potential incitants.[7] A striking feature of AP is that in spite of severe discomfort, no skin changes are visible.

Transient "blotchy" erythema has occasionally been noted.[7] Of the patients from whom data are available, over half had no reportable concurrent cutaneous abnormalities. Acne vulgaris, localized eczema, tinea pedis, and solar elastosis were each noted in two patients; facial telangiectasias, herpes zoster scarring, psoriasis, vasomotor instability, and xerosis were noted in one patient each.[7] In patients with eczema or xerosis, AP appeared in clinically normal skin, in anatomic sites away from the areas of eczema or xerosis. No consistently current or past general medical problems have been noted in AP patients. No drugs have been implicated, and no characteristic hematologic, serum chemistry, or serologic laboratory abnormalities have been noted. IgE and serum C3 levels have been normal.[9]

Mood changes are common during bouts of AP. More than half of our patients stated they felt aggressive, agitated, angry, irritable, or depressed after water contact. Indeed, many isolated themselves from others after bathing, or bathed only when alone at home to avoid unnecessary interpersonal conflict. Because of this obvious mood change, the spouses and children of these subjects often knew that the patient had recently bathed. The cause of these emotional changes is unknown. Although it is possible that some circulating substance(s) released as a result of water contact is responsible for inducing these mood changes, it is more likely that the emotional lability is related to the intense, generalized, and unremitting pruritus these patients must endure from 10 minutes-2 hours after each bath, shower, or swim.

The combination of severe skin discomfort, no observable skin changes, and, in some cases, transient mood swings simply from water contact has resulted in some AP patients being labeled as "neurotic" by physicians unaware of the existence of the condition. Many patients are greatly relieved to learn that their symptoms are not psychogenic and that there are other documented cases of the same condition.

The pathophysiology of AP is unclear, al-

though it is apparent that water, not other liquids, is the incitant. Haustein applied both ethanol and acetone to his three patients' skin and neither induced discomfort.[9] Greaves has also noted similar findings (Greaves MW, personal communication). Interestingly, Haustein noted that the application of water after either ethanol or acetone application resulted in greater than usual pruritus.

Greaves et al. noted that, although the total number of mast cells in their patients' skin was essentially normal, a significant increase in mast cell degranulation was present prior to water exposure. The degranulation increased still further following water challenge. Moreover, two of their three patients had elevations in blood histamine prior to water exposure, and all three showed increased blood histamine levels following water challenge.[6] It was postulated that these baseline elevations in mast cell degranulation and blood histamine were due to normal sweating, and that perhaps water challenge induced still further increases in mast cell degranulation. It is unlikely, however, that histamine release alone can account for the symptoms of AP. First, the injection of histamine 1:10,000 intradermally results in no exaggerated wheals or pruritus in AP patients.[9] Second, although histamine release into the skin may induce pruritus, many AP patients report a cutaneous sensation distinctly different from itching. In addition, both H_1 and H_2 histamine antagonists fail to significantly relieve the symptoms of AP.

Preliminary data suggest that acetylcholine release may play a role in the development of AP. Greaves et al.[6] applied hyoscine (an acetylcholine antagonist) to the skin of two of their patients prior to water challenge. After water exposure, the treated sites remained asymptomatic while the surrounding skin produced discomfort. Haustein noted a similar diminution in the severity of AP after application of 9% scopolamine (hyoscine) prior to water contact; however, the injection of acetylcholine 1:20 intradermally in his three patients resulted in no abnormal pruritus or wheals.[9]

Lotti et al. have reported that patients with AP exhibit markedly increased levels of cutaneous fibrinolytic activity (CFA) both before and after water challenge. This was first noted in a single patient[8] and reconfirmed in four patients.[12] In the latter, euglobulin lysis times (a measure of circulating fibrinolytic activity) were normal in all four patients prior to water challenge. The increased CFA in the skin specimens could be blocked by epsilon-amino-caproic acid. This suggests that the elevated CFA is due to plasminogen activator activity and not other proteases. It has been previously shown that experimental wheals induced by the intradermal injection of histamine and acetylcholine have increased CFA.[13]

Finally, Haustein reported that repeated tape stripping of symptomatic skin in AP patients results in no change in the degree of pruritus on water challenge.[9] This perhaps suggests that the area of the skin participating in the induction of AP probably lies below the stratum corneum.

The mechanism by which water induces AP is unknown. With the limited data now available, only speculative hypotheses can be proposed. Water contact may induce AP via percutaneous absorption of an unknown substance or substances through or from the epidermis. Or to explain why certain other physical stimuli, such as skin cooling, can also elicit discomfort, water or other stimuli may cause structural changes in the skin. Either the absorbed substance or the structural skin change may then, directly or indirectly, induce acetylcholine release from cutaneous sympathetic nerve endings. This in turn may lead to the release of histamine and other mast cell mediators. Then, raised levels of histamine and acetylcholine could explain the increased CFA. The absence of observable skin changes in AP might be explained by the slow, persistent release of histamine in the skin, perhaps induced by normal sweating. This may create a chronic state of tolerance or may prevent the development of threshold concentrations of histamine sufficient to induce wheals, even with water challenge.

No consistently effective therapy for AP has yet been found. Of 37 patients treated with H_1 and/or H_2 antihistamine agents,[7,9] none reported significant diminution of symptoms, and only 19 reported partial relief of their discomfort. Ultraviolet light therapy may help

some patients, although no controlled trials have been completed. Eight of 14 patients responded favorably to suberythematous doses of ultraviolet B light (UVB) (290-320 nm) given three times weekly. Seven noted significant relief and one reported partial relief. It was necessary to continue therapy three times weekly to maintain the benefit. Most patients reported a relatively prompt return of symptoms if UVB therapy was decreased in frequency or discontinued. Seven of 22 English patients reported that sunbathing decreased the intensity of their discomfort.[7] No results of PUVA therapy have been reported. Each of Haustein's three patients remained free of discomfort in skin areas covered with petrolatum ointment prior to water contact; areas of skin unprotected by the ointment became symptomatic following water contact.[9] Four other patients reported that the use of bath oils or emulsifying ointment in their baths decreased the severity of their discomfort.[7] Bayoumi and Highet[11] recently reported that sodium bicarbonate (baking soda) dissolved in the bath water abolished symptoms of AP in their two patients.

To date, only avoidance of unnecessary and excessive water contact can be recommended as an effective therapy for AP. A trial of UVB may benefit some patients, as may barrier ointments (such as white petrolatum or emulsifying ointment) and possibly sodium bicarbonate. Antihistamine therapy and bath oils may also provide partial relief.

As will be discussed below, the symptoms of AP bear a striking resemblance to those of PRV. Greaves has evaluated a patient who presented with symptoms typical of AP, but who on further evaluation was discovered to have PRV (Greaves MW, personal communication). It is thus advisable to follow patients with AP regularly for the possible development of PRV.

Polycythemia Rubra Vera

Pruritus without cutaneous signs is a common and characteristic complaint in patients with PRV. Of 325 untreated patients studied by the Polycythemia Study Group, 43% complained of significant pruritus.[14] Seventeen of 33 uncontrolled PRV patients reported by Gilbert et al.[15] experienced repeated episodes of generalized itching, as did 51 of 72 patients reported by Fjellner and Hagermark.[17] The pruritus of PRV characteristically occurs following a bath or shower, although it may occur spontaneously.[14,15] In many cases, hot water is a more potent incitant than warm or cold water.[16,17] Some patients experience discomfort following water contact at any temperature.[16] Fjellner and Hagermark[17] reported pruritus in association with hot baths in 38 of 72 patients, and five stated that even cold water contact would elicit discomfort. The discomfort began immediately on contact with hot water in two patients and immediately after a hot bath or shower in 28 patients.

The discomfort is not associated with any observable skin changes. The duration of pruritus following water exposure usually ranges from 15-60 minutes but may last as long as 2 hours.[17] It is typically prickling in character, in contradistinction to typical pruritus, and can be so severe and disturbing that patients avoid water contact and resort to infrequent regional sponge bathing.[15-17] The symptoms are often temperature dependent, frequently being induced by skin cooling. For example, some patients note similar prickling discomfort when undressing, getting into a cool bed at night, feeling warm and perspiring, or being exposed to cold ambient temperatures. In contrast to AP, the pruritus in PRV apparently becomes more intense if the skin is cooled.[16,17] Many patients are able to tolerate a hot bath or shower if they avoid skin cooling afterward.

Also in contrast to AP, therapy for the pruritus associated with PRV is often successful. Pruritus may subside with control of the hematologic dyscrasia, although there is no clear relationship between the severity of the polycythemia and the degree of discomfort. As many as 20% of patients continue to experience pruritus despite control of their polycythemia.[18] Pruritus, including WIP, may precede the diagnosis of PRV by 1-10 years.[17] It is thus possible that some patients diagnosed as having AP may eventually manifest signs of PRV.

As with AP, the cause of the pruritus in PRV

is unknown. Several possible mechanisms have been proposed. Iron deficiency may play a role because almost all patients with PRV have some degree of it as determined by bone marrow iron levels.[14] In an uncontrolled trial, Salem et al.[19] reported that oral iron therapy either eliminated or greatly reduced the pruritus, which they demonstrated in six of six iron-deficient PRV patients in whom pruritus had continued despite control of their polycythemia. The pruritus began to abate within 2–10 days and was completely gone within 2–3 weeks. Three other patients have experienced a beneficial effect from iron therapy.[20–22] Unfortunately, in one of these cases[22] (as in three of Salems' six patients), iron therapy had to be discontinued because of unacceptable elevations in red blood cell counts, and the pruritus recurred. It is not known by what mechanism iron deficiency contributes to the pruritus, neither is it known why iron therapy is of benefit.

Elevations in blood and urine histamine have been reported in uncontrolled PRV patients by Gilbert et al.[15] They found 22 of 33 patients with uncontrolled PRV to have raised blood histamine levels, whereas in controlled PRV patients only 2 of 30 had abnormally elevated blood histamine. Fifty-two percent of the uncontrolled PRV patients, as opposed to only 20% of the treated PRV patients, complained of pruritus. It is not specified, however, whether the histamine determinations were obtained during attacks of pruritus or which patients were experiencing water-induced pruritus. Steinman et al.[22] recently measured blood histamine levels and CFA before and after water challenge in a patient with PRV and water-related pruritus. Normal levels of blood histamine were noted prior to water challenge, whereas elevated levels were noted following water exposure. Moreover, markedly elevated levels of CFA were noted both before and after water challenge. Both of these findings are similar to those noted in patients with AP.[6,8,12] This suggests that increased histamine levels may be associated with the onset of pruritus in PRV patients, and that water contact may induce this increase in blood histamine. These findings require confirmation with a larger number of PRV patients. Similarly to AP, in which elevations in histamine may be associated with the pruritus, it is unlikely that histamine alone mediates the discomfort. Treatment with H_1 histamine antagonists is usually unsuccessful,[18] while the results with cimetidine (H_2 histamine antagonist) are variable. Easton and Galbraith[23] and Hess[24] reported complete relief or significant improvement of pruritus in one and two patients, respectively. Weick et al.[25] treated 34 patients with 300 mg of cimetidine three times daily for 30 days; 32 had controlled PRV (hematocrit <45) so that any relief of pruritus could be ascribed to the medication, not to a decrease in red cell mass. Two patients discontinued the medication because of increased discomfort. Fifteen patients showed improvement, and 12 reported complete relief of pruritus.

Cyproheptadine (histamine and serotonin antagonist) has been shown to be effective in treating PRV-associated pruritus. Gilbert et al.[15] reported that 15 of 18 patients treated with cyproheptadine (4 mg three to four times daily) noted improvement. Twelve of 18 experienced complete relief of both water-induced and spontaneous pruritus. In three additional patients, spontaneous pruritus resolved and post-bathing discomfort diminished in severity and duration. Another patient noted relief of pruritus but discontinued therapy because of side effects.

Pizotifen, a drug used in migraine prophylaxis, also possesses potent antihistamine and antiserotonin activities. Fitzsimons et al.,[26] in a placebo-controlled crossover study, reported that six of nine patients noted lessening of their pruritus with pizotifen. This suggests that serotonin may play a role in the pruritus.

Fjellner and Hagermark[17] suggested that serotonin and prostaglandin E2 (PGE2) act as mediators of pruritus in PRV. Both prostaglandins[27] and serotonin[17] may induce pruritus. In a double-blind, placebo-controlled crossover study, they showed that aspirin relieved pruritus to a greater degree than did placebo in 14 of 17 patients and totally relieved the pruritus in an additional patient. Aspirin inhibits prostaglandin synthesis and platelet aggregation. They also performed intradermal injections of serotonin and PGE2 singly and together into normal controls. The combination of sero-

tonin and PGE2 was significantly more pruritogenic than either substance alone. PGE2 is also known to lower the threshold of human skin to histamine-induced itching.[27] Both serotonin and PGE2 are released as a result of the aggregation of platelets. As previously mentioned, the pruritus in PRV is related to skin cooling. This made Fjellner and Hagermark hypothesize that skin cooling may induce vasoconstriction as well as catecholamine release from cutaneous sympathetic nerve endings, perhaps inducing subsequent platelet aggregation and release of serotonin and PGE2.

Finally, cholestyramine was reported to alleviate the pruritus in two patients.[16] One patient noted complete relief, while the second experienced significant improvement. The significance of this finding is unclear, as Fitzsimons et al. noted elevations in serum conjugated bile acid concentrations in only one of eight patients who complained of pruritus. Two other PRV patients with even higher concentrations of conjugated bile acids did not have symptoms of pruritus.[26]

Aquagenic Pruritus of the Elderly

In a recent review, Kligman[28] described a group of elderly institutionalized patients with persistent senile xerosis who experienced severe itching following water exposure. He labeled the condition aquagenic pruritus of the elderly (APE). Other patients with equal xerosis did not have water-induced itching. APE differs in many significant respects from AP and PRV, its only similarity being the water-related itching. Only warm or hot water seems to induce the pruritus, and prolonged immersion in water is required. Exercise, emotional upset, and hot ambient temperatures did not induce symptoms.

The severity of the pruritus increased with age, with the onset usually after 60 years of age. Moreover, the itching was directly proportional to the degree of dryness of the skin. Not unexpectedly, pruritus was more severe during winter months, due to the high indoor ambient temperatures and low humidity caused by central heating. Although the total number of patients evaluated is not specified, 75% were reported to be women. As with other xerotic patients, pruritus could also be induced by light stroking, changes in ambient temperature (such as removing clothing), or wearing rough clothing. The most significant cause of itching in these patients, however, was a hot bath; showering was less consistent at inducing symptoms.

Itching in APE does not begin until after emerging from the bath, and the severity of pruritus is directly related to the duration of water contact. Baths of less than 5 minutes do not induce significant symptoms. Application of cold, warm, or hot water compresses does not induce pruritus. Itching usually begins on the legs and progresses to the thighs, then the trunk and arms. It usually lasts from 10-20 minutes but can last an hour or longer. The severity of itching is related to the speed of drying after water immersion. Forced warm air drying is more pruritogenic than is towel drying. Thus, perhaps hydration of the skin followed by rapid drying results in pruritus. Indeed, the most severe itching occurred after removal of plastic wrap that had been applied to one leg for 1-3 days. The condition is chronic and exacerbations are frequent.[28]

Eight patients were studied in greater detail. None was dermographic. The wheals and pruritus induced by the intradermal injection of 0.1 ml of 1:10,000 histamine phosphate did not differ from those in four controls. Local application of wet compresses failed to induce itching. Immersion of one leg in water of varying temperatures (15-45°C) for varying lengths of time resulted in pruritus limited to the area of water contact after drying. With higher water temperatures and longer contact, the itching developed sooner, was more intense, and lasted longer. Attempts to induce tolerance by repeated immersions 5 days weekly for 2 weeks were unsuccessful. The administration of one minimum erythema dose of ultraviolet light (280-340 nm) to one leg three times weekly for 3 weeks did not reduce the severity of water-related pruritus. Biopsy specimens were taken from the symptomatic skin of three APE patients and from three controls with equally severe xerosis without pruritus. The specimens

were stained for mast cells, elastic fibers, glycosaminoglycans (Mowry's stain), and small vessels (alkaline phosphatase). No significant differences between the two groups were noted.

Therapy of APE should be directed at controlling the cutaneous xerosis. In Kligman's series, systemic H_1 (with or without H_2) antihistamines, tranquilizers, hypnotics, and topical corticosteroid preparations were not helpful. Relief of itching was proportional to improvement in xerosis. Twice-daily application of petrolatum and lanolin was the most effective topical regimen. Water-in-oil emulsions were almost as effective and were more acceptable to the patients. Oil-in-water creams, though more cosmetically acceptable, were less effective. Other beneficial adjunctive measures included avoidance of harsh soaps, avoidance of water immersion, substitution of brief sponge baths or showers for baths, and avoidance of the prolonged use of moisturizers containing potential irritants (such as >2.5% crude coal tar, 20% propylene glycol, 5% salicylic acid, or 20% urea). These agents may be of benefit initially, but their chronic use eventually leads to skin irritation.

References

1. Logan RA, Feher MD, Steinman HK. The prevalence of water-induced itching. Br J Dermatol. 1984;111:734-736.
2. Wong RC, Fairley JA, Ellis CN. Dermographism: a review. J Am Acad Dermatol. 1984;11:643-652.
3. Jorizzo JL, Smith EB. The physical urticarias: an update and review. Arch Dermatol. 1982;118:194-201.
4. Warin RP, Champion RH. The physical urticarias. Maj Probl Dermatol. 1974;4:120-160.
5. Shelley WB. Questions and answers. JAMA. 1970;212:1385.
6. Greaves MW, Black AK, Eady RAJ, et al. Aquagenic pruritus. Br Med J. 1981;282:2008-2010.
7. Steinman HK, Greaves MW. Aquagenic pruritus. J Am Acad Dermatol. 1985;13:91-96.
8. Lotti T, Cappugi P, Lattari P, et al. Increased cutaneous fibrinolytic activity in a case of aquagenic pruritus. Int J Dermatol. 1984;23:61-62.
9. Haustein UF. Aquagener pruritus. Dermatol Monatsschr. 1984;170:564-566.
10. Lubach D. Aquagener pruritus sine materia. Hautarzt. 1984;35:600-601.
11. Bayoumi A-HM, Highet AS. Baking soda baths for aquagenic pruritus. Lancet. 1986;2:464.
12. Lotti T, Steinman HK, Greaves MW, et al. Increased cutaneous fibrinolytic activity in aquagenic pruritus. Int J Dermatol. 1986;25:508-510.
13. Ryan TJ. Microvascular injury. Maj Probl Dermatol. 1976;7:49.
14. Berlin NI. Diagnosis and classification of the polycythemias. Semin Hematol. 1975;12:339-351.
15. Gilbert HS, Warner RRP, Wasserman LR. A study of histamine in myeloproliferative disease. Blood. 1966;28:795-806.
16. Chanarin I, Szur L. Relief of intractable pruritus in polycythaemia rubra vera with cholestyramine. Br J Hematol. 1975;29:669-670.
17. Fjellner B, Hagermark O. Pruritus in polycythaemia vera: treatment with aspirin and possibility of platelet involvement. Acta Derm Venereol (Stockh). 1979;59:505-512.
18. Wasserman LR. The treatment of polycythemia vera. Semin Hematol. 1976;13:57-78.
19. Salem HH, Van Der Weyden MB, Young IF, et al. Pruritus and severe iron deficiency in polycythaemia vera. Br Med J. 1982;285:91-92.
20. Sneddon IB, Garretts M. The significance of low serum iron levels in the causation of itching. In: Jadassohn W, Schirren CG, eds. Proceedings of the XIII International Congress of Dermatology, Munich. Berlin: Springer. 1968:1061-1063.
21. Vickers CFH. Nutrition and the skin: iron deficiency in dermatology. In: Ledingham JCG, ed. Proceedings of the tenth symposium on advanced medicine. London: Royal College of Physicians. 1974:311-315.
22. Steinman HK, Kobza-Black A, Lotti TM, et al. Polycythaemia rubra vera and water-induced pruritus: blood histamine levels and cutaneous fibrinolytic activity before and after water challenge. Br J Dermatol. 1987;116:329-333.
23. Easton P, Galbraith PR. Cimetidine treatment of pruritus in polycythemia vera. N Engl J Med. 1978;299:1134.
24. Hess CE. Cimetidine for the treatment of pruritus. N Engl J Med. 1979;300:370.
25. Weick JK, Donovan PB, Najean Y, et al. The use of cimetidine for the treatment of pruritus in polycythemia vera. Arch Intern Med. 1982;142:241-242.
26. Fitzsimons EJ, Dagg JH, McAllister EJ. Pruritus of polycythaemia vera: a place for pizotifen? Br Med J. 1981;283:277.
27. Greaves MW, McDonald-Gibson W. Itch: role of prostaglandins. Br Med J. 1973;3:608-609.
28. Kligman AM, Greaves MW, Steinman HK. Water-induced itching without cutaneous signs: aquagenic pruritus. Arch Dermatol. 1986;122:183-186.

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