Treatment of Urticaria

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Urticaria is not a single entity with only one cause or treatment. Rather, it comprises a group of conditions with wheals or angioedema. Many inflammatory mediators have been implicated in causing urticarial lesions including kinins, acetylcholine, fibrinolysin and Hageman factor, but histamine from mast cells and basophils is generally involved. Therefore, an understanding of mast cell function and histamine metabolism helps greatly in the management of the patient with urticaria.

PATHOPHYSIOLOGY

Mast cell degranulation can be induced by either immunologic or nonimmunologic stimuli, but in either case the initial event probably occurs on the cell surface, and histamine is released by exocytosis with a change in the plasma membrane.[15] Histamine release is accompanied by increased levels of diacylglycerol (a phospholipid precursor that probably aids membrane fusion) and arachidonic acid.[71] The mast cell surface has receptors that can lead to degranulation, including receptors for the Fc portion of IgE[19, 54, 55, 78] and for a variety of nonimmunologic stimuli including drugs, polycations, and enzymes. Changes in the cell membrane take place before and during mediator release,[72] and these are modulated by the levels of cyclic adenosine 3′,5′-monophosphate (cAMP).[73]

In Type I or anaphylactic reactions, IgE forms ligands on the cell surface by attachment of the Fc fragments, and two of these molecules are bridged by antigenic material. This perhaps activates a number of membrane-associated enzymes, including many associated with phospholipid metabolism.[56] Next, a complex series of events occurs involving a serine esterase, cellular uptake of calcium, and the utilization of energy.[56, 66]

Microtubules are important to histamine release.[35, 36, 66] These structures and tubulin, the building material for their formation, are in a dynamic state of equilibrium with the relative quantity of each modulated by cyclic nucleo-

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tide levels (Fig. 1). Microtubule assembly is potentiated by cyclic guanosine 3′,5′-monophosphate (cGMP), while cAMP promotes disassembly. Synthesis of cAMP follows stimulation of receptors for prostaglandin E, beta$_2$ adrenergic agonists,[9] and histamine H_2 agonists,[118] while GMP synthesis and histamine release increase in response to muscarinic agents[64] and histamine H_1 agonists.[118] Histamine tends to inhibit its own secretion largely through stimulation of H_2 receptors by increasing levels of cAMP.[86] However, released histamine also stimulates H_1 receptors, causing a greater percentage increase in cGMP.[118] The overall effect may or may not be detrimental, but, if it is, this would help explain some of the engimas in chronic urticaria.

The level of cAMP is also under the control of its natural inhibitor, a phosphodiesterase. Methylxanthines, such as theophylline, block the breakdown of cAMP by its phosphodiesterase, resulting in increased levels of cAMP and a reduction in histamine release. Alpha adrenergic agents cause reduction of cAMP levels (which would be unfavorable)[9] but also cause vasoconstriction, which, in urticaria, is symptomatically beneficial.

Exchange of calcium across the cell membrane is also modulated by the level of cAMP.[65] However, histamine secretion induced by compound 48/80, an experimental drug causing nonallergic release of histamine, does not require external calcium probably because of a mobilization of internal calcium stores. Calcium has been used in the past to treat certain types of vascular reactions because histamine release is mediated in a narrow range of calcium concentration (10^{-7} to 10^{-5} mol), and higher concentrations may be inhibitory.[5]

Once histamine is liberated, it participates in many activities, the best known of which is its effect on the surrounding vasculature and smooth muscle tissue. Lewis described a triple response which comprises initial erythema from dilatation of capillaries and venules;[85] the surrounding flare is due to arteriolar dilation mediated by an axon reflex, and the local edema is the result of increased vascular permeability.[7] Response to intradermal histamine is reduced by both H_1 and H_2 blockers,[92, 125] although the latter does not provide protection to all three components from compound 48/80[92] or under all protocols.[43] Therefore, both H_1 and H_2 blockers can be expected to inhibit the blood vessel response to released histamine or experimentally induced urticaria, but naturally released histamine causes a feedback (inhibitory) effect on mast cells and basophils;[86, 118] this may help to explain the mixed reviews received by therapeutic programs combining H_1 and H_2 antihistamines.

Released histamine is inactivated in vivo through either of two pathways: the diamine oxidase (histaminase) pathway, and the histamine-N-methyl transferase and monoamine oxidase pathway.[9] In the former, the terminal enzymatic step is inhibited by therapeutic doses of aspirin[9] and salicylates.[110] The initial enzymatic step of the latter, methylation of histamine, is reduced by antimalarials.[16]

Outside factors (other than specific antigenic materials) thought to adversely influence urticaria include vasodilatory stimuli,[106] direct histamine releasing agents,[162] inhibitors of prostaglandin E synthesis, beta$_2$-adrenergic blockers, muscarinic agonists,[10] and a variety of dyes, preservatives, and chemicals.[100, 126, 162]

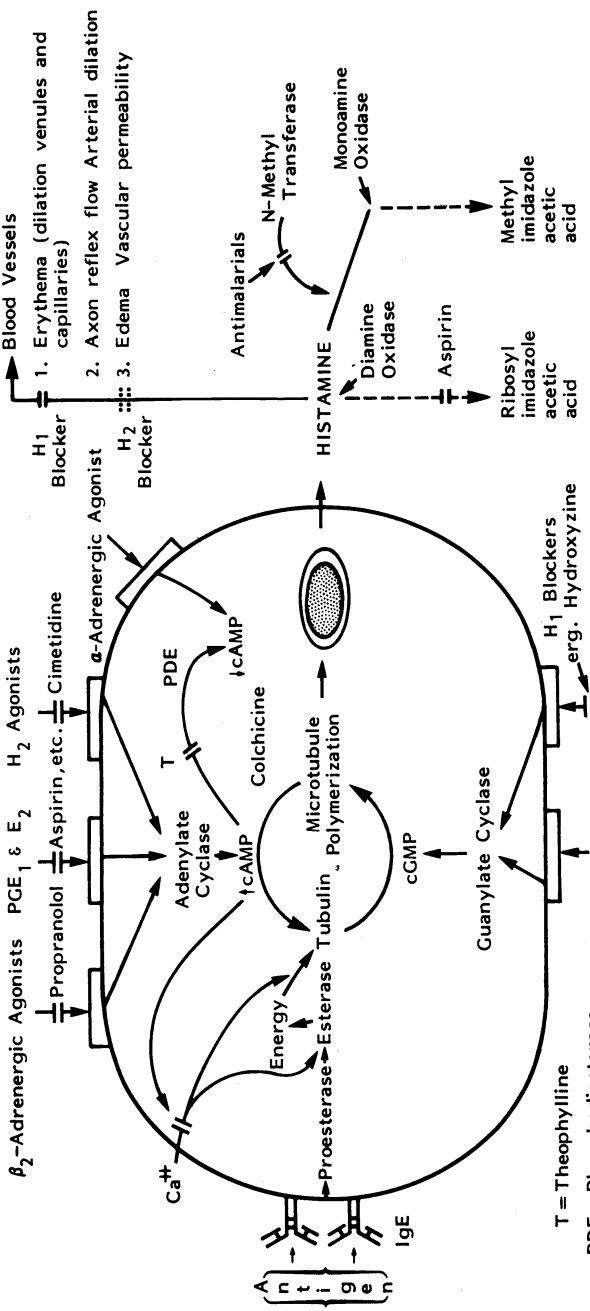

Figure 1. A concept of mast cell release in urticaria.

DIET, DYES AND DIVERSE OUTSIDE INFLUENCES

The typical patient with acute urticaria caused by food allergy usually makes the proper diagnosis without the help of a physician, but those with food-aggravated chronic urticaria represent a challenging therapeutic problem. Many drugs, dyes, and preservatives may aggravate urticaria by nonallergic histamine release, and a diet low in salicylates, azo dyes, and benzoates helps an impressive percentage of patients with urticaria,[126] as does a low yeast diet.[48, 49, 61]

Histamine Releasing Agents

Histamine releasing agents include antibiotics, such as stilbamidine, polymyxin and chlorotetracycline, quinine, various opiates, amphetamines, atropine, antazoline, hydralazine, tolazoline, polymyxin B, curare derivatives, and even thiamine and alcohol. Other direct histamine releasers include shellfish and lobster, bacterial toxins, snake venom, jellyfish and proteolytic enzymes, especially following exposure to Portuguese man-of-war and various caterpillars.[38, 106, 114, 115, 156, 162] Although normal individuals require quantity to cause urticaria,[162] less may be effective with active disease, and the effects are probably additive. Perfumes or flavors containing cinnamic aldehyde, cinnamic acid, benzaldehyde, or the preservative benzoic acid are also in this category.[28] Benzoic acid compounds can often be avoided by reading labels on foods. Possible sources are fruit drinks, jelly and gelatins, cheese preparations, and refrigerated preserves of various fish and seafoods.[162]

Aspirin and Salicylates

While aspirin can certainly cause urticaria on an allergic basis, the principal effect of aspirin[77] and the nonsteroidal anti-inflammatory agents on histamine release is probably not allergic[151] but is the result of enhancement.[172] The reported incidence of flares of urticaria[14, 23, 60, 109, 161] and positive scratch test response to aspirin, tartrazine, and benzoic acid[100] would be better explained by a pharmacologic rather than an immunologic response. Challenging patients with chronic urticaria with aspirin does not aggravate the condition in all, or even most persons. Reports vary, but 21 to 41 per cent of patients may show an exacerbation,[14, 60, 109, 161] and exacerbation is more common with severe urticaria[14] and with increased dosage.[59] Challenge causes bronchoconstriction in aspirin-sensitive asthmatic patients but hives in patients with urticaria.[134] The delay in flares of several hours after aspirin ingestion,[162] the day-to-day variability of results said to follow oral challenge,[80] and the failure to induce the disease months after recovery all suggest a nonallergic mechanism.

Aspirin has more than one site of activity in the synthesis and subsequent metabolism of histamine. It inhibits synthesis of prostaglandin E by cyclooxygenase reducing cyclic AMP production,[9] and this activity can be expected from almost all the nonsteroidal anti-inflammatory agents as well. Aspirin also influences one step in the histaminase pathway of histamine catabolism.[10]

The effect of salicylates on histamine release is controversial.[23, 59, 131, 147] While some argue that they are not a problem for urticaria patients, Moore-Robinson and Warin found that 13 of 18 patients known to react to aspirin also reacted to salicylates.[109] The discrepancy between aspirin and (other) sali-

cylates may be due to a difference in effective dosage,[59] as the number of reactors grows with increased challenge. Avoidance of aspirin is said to be followed by improvement in 51 per cent of patients (and an even greater number of those responding to oral challenge),[60] but the effect of a low-salicylate diet alone is not clear. It is virtually impossible to totally remove a patient from all exposure to dietary salicylates,[147] but the important consideration is probably quantitative so avoidance of salicylates and other aggravating substances is in order. Wintergreen flavoring is produced by methyl salicylate, which should be avoided. Topical salicylic acid can cause contact urticaria.[158] Published salicylate-poor diets[13, 87, 112] may or may not exclude tartrazine.

Azo Dyes

Tartrazine, or FD&C Yellow No. 5, and certain other azo dyes have been implicated as causing or aggravating urticaria.[23, 100, 109] The incidence of responders ranges from most[100] to only a few of those "sensitive" to aspirin.[127, 166, 172] Michaelssohn and Juhlin found that a high percentage of persons with chronic urticaria had a positive reaction when scratch tested with aspirin, benzoic acid preparations, and tartrazine.[100] Some investigators have ascribed tartrazine-induced urticaria to a cross-reaction with salicylates. While both immediate hypersensitivity[155] and anaphylactoid purpura[99] have been reported, the mechanism by which tartrazine aggravates asthma, urticaria, and so forth is not known. The chemical structure of tartrazine does not suggest that it would cross-react with aspirin, and some pharmacologic actions parallel those of aspirin. Most tartrazine reactions are not likely mediated by IgE,[167, 168] although reagin-mediated hypersensitivity can be produced experimentally in animals.[102] A specific IgD can be found by radioimmunoassay,[167] but there is no indication that it is causally related. The pharmacologic reaction is probably not a direct histamine release,[76] as has been suggested, but it may augment reactions due to other causes. Tartrazine has the same effect on platelet adhesion as aspirin, but, unlike aspirin, neither that mechanism[31] nor the adverse effect in asthma[53, 157] is mediated through inhibition of prostaglandin synthesis.

The potential sources of this dye are legion. Many drugs used to treat urticaria[3] and asthma have contained tartrazine. Tartrazine-free coloring agents are now used in Atarax (hydroxyzine hydrochloride) and Periactin (cyproheptadine hydrochloride),[81] but it may be possible to obtain older supplies of some forms of these drugs that contain FD&C Yellow No. 5.

Candies contain up to 285 mg of tartrazine per kg and pudding mixes up to 1223 mg per kg.[171] Widespread use[3] of FD&C Yellow No. 5 plus a recent plethora of reports of adverse effects prompted the Food and Drug Administration to require labeling of food and medications containing tartrazine manufactured after June 1980,[27] and this regulation has greatly facilitated patient adherence to a low tartrazine diet. Lee et al. have recently published a relatively comprehensive list of drugs known to contain tartrazine as well as a list of manufacturers that no longer use it.[81]

Tyramine and the Yeast-Free Diet

Tyramine is a phenolic amine that occurs in higher concentrations in protein foods, such as lobster and scallops, as well as in foods altered by bacteria, yeast, or mold. It has been associated with hypertensive encephalopathy in

persons taking monoamine oxidase inhibitors as antidepressants and has been suspected of being an aggravating factor in migraine headaches.[12, 44] Chronic urticaria is aggravated by food yeast and *Candida albicans* extract, especially in patients with a positive scratch test to Candida,[61] but as Warin and Champion point out,[162] the foods high in tyramine[97] closely resemble those excluded by the "low yeast" diet.[48, 162] Tyramine causes nonallergic histamine release,[115] and it shares one catabolic enzyme with histamine. Patients with positive scratch tests to *C. albicans* are more likely to flare upon oral challenge than those with a negative test, but they also have more reactions to unrelated antigens and are little more likely to clear with anti-Candida therapy.[61] Anti-Candida therapy combined with a "low yeast" diet improves a respectable percentage of those with negative scratch tests, although it is more often totally effective in those with a positive skin test.[61]

The histamine-releasing property of tyramine[116] may be responsible for reported problems with those foods. Tyramine may also affect alpha adrenergic uptake locally[37] and may compete for monoamine oxidase activity in one of the two pathways of histamine metabolism.

MANAGING THE PATIENT WITH URTICARIA

Clinical Evaluation

While most urticarial eruptions may seem the same to the uninitiated, careful evaluation of the eruption and other clinical features often allows proper clinical diagnosis and classification. The urticarial conditions caused by physical stimuli may be suspected, if not identified, by factors such as appearance and location, and the presumptive diagnosis can then be confirmed by the history and appropriate diagnostic tests. The shape of lesions is striking in dermographism, tiny wheals with large flares are typical in cholinergic urticaria, and solar urticaria occurs in light-exposed sites.

Urticaria can be divided into allergic and nonallergic forms, and, more importantly, the former can be divided into Gell and Coombs' Type I (anaphylactic) and Type III (urticarial vasculitis) reactions. Reagin-mediated (Type I) reactions may be accompanied by rhinorrhea, wheezing, and other symptoms including, in severe cases, an anaphylactic reaction. In Type I (IgE) urticarial reactions to food, the timing of the eruption and the shorter duration compared with Type III eruptions help to confirm suspicions raised by the history.

Urticarial vasculitis[13a, 89, 104, 105, 117, 140, 142] may accompany hepatitis B infections, infectious mononucleosis, drug eruptions, anaphylactoid purpura, lupus erythematosus, and other rheumatologic conditions, to name a few. Here lesions tend to persist 24 to 72 hours, resolve with residual findings (such as pigmentation, scaling, and purpura), and are often said to burn rather than itch. Angioedema is often present and arthritis is common. Gastrointestinal symptoms, fever, adenopathy, neurologic disorders, asthma, Raynaud's phenomenon, erythema multiforme–like eruptions, livedo reticularis, and other signs of vasculitis may also be seen. Monroe has recently grouped the similar,[104] but seemingly heterogenous[89, 105, 117, 140, 142] reported forms of urticarial vasculitis.

Taking a History

Traditionally physicians consider history taking to best be done person to person, but in urticaria the use of printed forms is often more thorough and is certainly more cost effective. Excluding psychosomatic influences, a "cause" can be found in a very small percentage of patients with chronic urticaria.[41] However, a thorough evaluation of every patient is in order because a cause is sometimes found, and by use of a well-designed printed form aggravating influences are uncovered that the patient and physician might not otherwise suspect. These might include causes of vasodilatation and use of histamine-releasing agents, known sources of food dyes, salicylates, tyramine, benzoic acid, and other derivatives of balsam of Peru. A search for psychosomatic influences can often be done more effectively in person, because communicating an understanding of the patient's problem helps to gain cooperation, if not objective improvement.

The most important item is the drug history. The patient should not only write the names of all drugs taken, but should bring in *all* medications taken and should complete a checklist suggesting items frequently overlooked, such as laxatives, vitamins, over-the-counter medications, headache remedies, artificial sweeteners, and topical medicaments.

Laboratory and Clinical Testing

Lists of helpful tests are available,[106] but testing should be based on the history and physical findings and should not done as a blind screen.[58, 62] Routine scratch testing is seldom helpful,[14] although intradermal testing for immediate reactions (rather than the usual delayed reading) to Candida and trichophytin may correlate clinically with a response to a "low yeast" diet.[61] Methods for uncovering foci of infection are available,[103] but Juhlin,[62] in a study of 334 patients, concluded that routine laboratory tests and x-ray films of sinuses and teeth are of little value in recurrent urticaria. Jacobsen felt that type of testing was not cost effective, with the possible exception of sinus films.[58] Even there, the likelihood of success should be higher in persons with a history of allergic rhinitis or sinusitis. Therapeutic trials of antibiotics have been recommended as a means of locating hidden causes of urticaria.[2] However, Juhlin did not find antibiotics to be very effective, and removal of dental foci helped only 3 of 10 well selected patients.[62]

The laboratory is often more helpful in diagnosing urticarial vasculitis, in which an elevated erythrocyte sedimentation rate and a biopsy picture of venulitis[142] are especially helpful. The histopathologic picture includes endothelial swelling of venules, fibrinoid deposits, extravasation of erythrocytes, a perivascular infiltration rich in neutrophils, and leukocytoclasis. Monroe et al. found that 20 per cent of patients with urticaria had vasculitis on biopsy.[105] Obviously the search for causative factors and the treatment are somewhat different than in the other forms of urticarial eruptions. Urinalysis, complement determinations, circulating immune complexes, direct immunofluorescence, hepatitis B antigen, heterophile agglutination, cryoglobulins, antinuclear antibody tests, rheumatoid factor, VDRL, and immunoglobulin levels are sometimes helpful.[104]

Cryoglobulins, cryofibrinogens, and a VDRL should be obtained in cold urticaria,[42, 153] but disagreement exists on cold hemagglutinins.[4, 42] Provocation tests such as the ice cube test for acquired essential cold urticaria can also help, particularly when the eruption is not present.

Appropriate direct examination for dermatophytes and Candida as well as culture should be done when indicated. Stool examination for parasites is not often positive but can be helpful in an occasional patient.[96] Therefore, the physician must be eclectic, selecting the proper tests based on the needs of that patient.

TREATMENT

CHRONIC URTICARIA

While the most obvious solution to the treatment of urticaria may be the removal of the patient from the cause of the eruption, it may not be possible to find an identifiable cause even with a diligent search.[14, 41] Practically any cause of cutaneous vasodilatation aggravates the eruption, and this must also be controlled. The use of antihistamines is said to be disappointingly ineffective at times,[80] and Shelley has recommended they be used with caution because they become a crutch to avoid the pains of a thorough work-up.[136] However, others regard them as effective in most such cases[41] and recommend that recurrent episodes of chronic, idiopathic urticaria other than vasculitis be treated by continuous and prophylactic administration of antihistamines.[145] When these agents fail to clear the eruption, the following have been recommended: use of another antihistamine from a different chemical group, combination of antihistamines from different groups,[106] matching the timing of the eruption to effective blood levels of the antihistamine,[162] avoidance of antihistamines with tartrazine coloring, and a combination of H_1 and H_2 blockers.[107] Blood vessels contain both histamine H_1 and H_2 receptors,[92, 125] with the axon reflex vasodilation and direct vasodilation being induced by H_1 and H_2 agonists, respectively.[125] The combination is helpful in experimental urticaria using injected stimuli.[52] In chronic urticaria improvement has been reported for combined treatment,[107] but others find little benefit.[18, 20] When one considers that H_2 blocking agents have a favorable,[92] but perhaps not marked[52] effect on the vasculature but a detrimental effect on cyclic nucleotide formation within mast cells,[9] it is not surprising that dermographism is benefited by their addition,[95] while reports from their use in chronic idiopathic urticaria are mixed.[18, 20, 69]

Antihistamines have been judged by their inhibition of the pharmacologic effects of histamine, but the affinity for mast cell H_1 receptors may also be important. Based on studies of affinity for such receptors on mouse neuroblastoma cells, cyproheptadine and hydroxyzine would lead the list of antihistamines on a molar basis.[124] The effectiveness in urticaria attributed to hydroxyzine[26, 30] may be partly the result of this property, especially considering the molar amounts used at therapeutic dosage.

The antihistaminic property of tricyclic antidepressants has recently been rediscovered. These agents contain in their structure an aminoethyl radical that provides antihistaminic effect, and some of them are extremely potent antihistamines. Compounds with tertiary amines are more effective than the ones with secondary amines, and those with unsaturated bonding at the 3 position of the propaneamine moiety seem to have higher coefficient of binding. The two characteristics appear to be additive since doxepin and amitriptyline have greater affinity for H_1 receptors than many other well-known tricylic antidepressants.[124] One recent study confirms the clinical effectiveness of tricyclic antidepressants as antihistamines.[150] The antihistaminic effect on the central nervous system has been used to explain the quality of drowsiness that complicates use of certain of these drugs.[124]

At the present time hydroxyzine and cyproheptadine would seem to be the therapeutic agents of choice in urticaria. Antihistamines that contain tartrazine (FD&C Yellow No. 5) as a coloring agent must be carefully avoided, but Atarax and Periactin (with the exception of older stocks) do not contain that dye. The publication by Lee et al. can be used as a guide to avoid tartrazine-containing medications.[81]

Epinephrine is temporarily helpful, particularly in acute urticaria, but terbutaline, a more specific $beta_2$ agonist, has been used successfully in combination with ketotifin in the treatment of chronic urticaria.[130] Both agents should increase cAMP levels within mast cells. Epinephrine has a favorable effect on the cutaneous vasculature and, overall, on cyclic nucleotide levels within mast cells. An additional benefit occurs in allergic urticaria because adrenalin, together with the antigen, induces a refractory state following mast cell degranulation.[10]

Systemic corticosteroids are not routinely used but may help acute urticarial eruptions of known cause or special situations such as a drug eruption or severe episodes of pressure urticaria. Calcium-channel blockers depress cellular uptake of that ion and benefit exercise-induced asthma,[113] but the total effect in asthma[90] and urticaria is not known.

A number of drugs that are known to be effective in asthma may also have some benefit in urticaria, but this is not as well documented. These would include theophylline, which inhibits breakdown of cAMP by phosphodiesterase,[10] and chromolyn sodium and doxantrazole,[11] which stabilize the mast cell in some uknown way.

Antihistaminic drugs are generally safe but drowsiness can be a problem, even precluding the use of an adequate dosage to control urticarial symptoms. Fortunately, tolerance to drowsiness often develops after a few days, provided treatment is not discontinued. Where a minimal amount of any effective antihistamine is not tolerated, hospitalization can occasionally be helpful.

That urticaria can be aggravated by changes in the cutaneous vasculature is well accepted.[106] Perhaps it seems obvious that vasodilating influences, such as heat, exercise, sunburn, vasodilating drugs, fever, and alcoholic beverages, are sometimes followed by sudden flares in previously well-controlled urticaria. However, it may not be so apparent even to an intelligent patient until he or she is told.

URTICARIAL VASCULITIS

In urticarial vasculitis treatment depends upon the underlying cause and might include such diverse approaches as antibiotic therapy for bacterial infections, nonsteroidal anti-inflammatory agents, or, in the case of a serum sickness–like drug eruption, even corticosteroids. Indomethacin, which inhibits production of prostaglandin E, may be expected to aggravate chronic urticaria, but it is helpful in treating urticarial vasculitis.[101] However, aspirin must be used with caution until an allergy to this substance is ruled out. Dapsone helped one patient with urticarial vasculitis caused by lupus erythematosus.[128]

PHYSICAL URTICARIA

Physical urticarias represent exceedingly diverse entities within a group united by the common finding of an urticarial response to physical stimuli. The incidence ranges from the extremely common dermographism to various rare and esoteric conditions such as aquagenic urticaria, solar urticaria, and hereditary angioedema.

Dermographism

Dermographism or factitial urticaria, found in 4.24 per cent of the population in one study,[74] is divided into simple dermographism, symptomatic dermographism which is pruritic, and red dermographism with diffuse whealing produced by rubbing rather than stroking the skin and demonstrated by stretching the skin.[164]

Treatment requires avoidance of vasodilatory influences, trauma, and pressure, and use of an oral (H_1) antihistamine with hydroxyzine[95] being the choice of most authorities. The addition of the H_2 blocker cimetidine[69, 94] is controversial. It actually increased itching in one study.[94] Aspirin apparently does not aggravate dermographism.[109]

The required duration of treatment varies considerably, and there is no way to accurately determine prognosis in a given patient. About one in five are clear without treatment after a year.[74] The disease begins more commonly in the younger age groups and seems to be less common after 55 years of age.[14]

Delayed dermographism[6, 67] is manifested by the appearance of wheals and deeper swelling 1 to 8 hours after stimulation. (Ordinary dermographism may appear and clear at the proper time prior to this.) Symptoms may last one or two days, and there is no known effective treatment. Patients with delayed dermographism may show delayed pressure urticaria,[6] and the symptomatology and perhaps the mechanisms overlap.[25, 162]

Dermographism also may occur during and following urticaria or as a reaction to insect bites and is a regular finding in lesions of some forms of urticaria pigmentosa (Darier's sign). Cholinergic urticaria with small wheals in a line of trauma has been termed cholinergic dermographism. Treatment of these entities should not be different from dermographism and cholinergic urticaria, respectively.

Hereditary Angioedema

Hereditary angioedema, caused by an absent or nonfunctioning C_1 esterase inhibitor, is characterized by local edema[29] following trauma such as dental manipulation and surgery.[33] This condition responds to androgenic agents[148] and worsens with progestens. Danazol[29, 34, 50, 163] and stanozolol[135] are effective, and the former is the treatment of choice for all phenotypes.

Delayed Pressure Urticaria

Delayed pressure urticaria is characterized by deep, painful wheals peaking 9 hours after exposure to pressure and proved by applying 136 gm or more per mm^2 to skin of the back for 5 seconds or longer.[25] The symptomatology reportedly overlaps with delayed dermographism.[25, 129, 162] The response in delayed pressure urticaria is dependent upon the pressure, duration, and anatomic area (of skin), and it is followed by a refractory period.[25]

Treatment of pressure urticaria leaves much to be desired. Depletion of cutaneous stores of histamine with compound 48/80[129] or a recent episode[25] provides a refractory state, but antihistamines are said to be without benefit. According to Warin and Champion,[162] Ryan found the condition in only 4 of 22 patients to be improved by the fibrinolytic agents, phenformin and ethylestrenol. Systemic corticosteroid therapy may temporarily control symptoms,[106] but this is probably best reserved for temporary use during periods of severe exacerbation.

Solar Urticaria

Solar urticaria comprises a heterogenous collection of erythematous and urticarial eruptions induced by ultraviolet A (UVA), ultraviolet B (UVB), or visible light, or a combination thereof. Recent classifications exclude urticaria induced by infrared radiation. Some cases of solar urticaria have been associated with systemic lupus erythematosus, porphyria cutanea tarda, erythropoietic prophyria, and even sulfonamide administration.[162] However, the chief differential is probably polymorphic light sensitivity in which plaques occur after hours or days rather than 15 or 20 minutes, while solar urticaria, where the primary lesion is a wheal, clears within approximately an hour.

Obviously, avoidance of unnecessary light exposure is advisable. Effective chemical and physical sunscreening agents carefully selected to provide protection in the spectrum of sensitivity may be of some benefit. Ramsey has reported "induction of tolerance" by repeated exposure to sunlight or appropriate artificial light sources.[120] This is apparently due to histamine depletion of cutaneous mast cells because similar local tolerance can be induced with the histamine depleting agent compound 48/80.[122] The beneficial effects of antihistamines,[57, 88] blood levels of histamine, and mast cell degranulation after challenge[45] tend to implicate histamine as a mediator in solar urticaria. Radioenzyme assay studies and the presence of eosinophilic chemotactic factor after UVB and visible light also implicate the mast cell.[144] However, Sams et al. failed to demonstrate histamine or kinins,[132] so the mechanism in all patients may not be the same. Hydroxyzine is sometimes beneficial.[123] Psoralens and sunlight[119] and chloroquine[24] have also been used to advantage. Beta carotene was shown not to help at least three patients.[75]

Essential Cold Urticaria

In the differential diagnosis of cold urticaria, one should consider the possiblity of symptomatic cold urticaria caused by cryoglobulinemia, cryofibrinogenemia, and paroxysmal cold hemoglobinuria.[4, 42] Cryoglobulinemia is occasionally associated with purpura, necrosis, and perhaps Raynaud's phenomenon. The rare possibility of urticaria from cold hemolysins in paroxysmal cold hemoglobinuria probably justifies obtaining a VDRL.

Essential cold urticaria is divided into familial and acquired types. The former, a rare condition inherited as an autosomal dominant trait, is characterized by urticaria one-half to three hours following a generalized exposure to cold sufficient to lower body temperature. On occasion it is associated with fever, chills, arthralgia, headache, and leukocytosis.[152, 153] No good therapeutic approach is available.

Essential Acquired Cold Urticaria. This condition, the most common form of cold urticaria, is characterized by wheals at the site of cold exposure and is readily produced within a few minutes by application of an ice cube to the skin. Mucous membranes are not immune and the bronchial mucosa can be involved in some patients breathing extremely cold air. Generalized hypotension, flushing, and angioedema following extreme exposure (such as immersion) may be caused by a generalized histamine release. Both IgE[51] and IgM[159] have been reported as transferable serum factors. Histamine release in this disease is well documented,[68] although it can be reduced by therapy without clinical improvement.[70] Dissociation of cold-evoked histamine release and urticaria following cold challenge has been shown, and other mediators have been implicated.[141, 165] Treatment with cyproheptadine[1, 39, 160] and avoidance of cold are helpful. Doxantrazole, a chromylin-like agent, is also effective.[11] Desensitization has been tried and may be beneficial.[82, 121]

Three new clinical forms of cold urticaria include a dominantly inherited form of delayed cold-induced urticaria,[143] cold urticaria with persistent wheals,[63] and cold reflex urticaria.[21] Patients with delayed cold urticaria respond with urticarial wheals 9 to 18 hours following application of ice. The mechanism of this reaction is unclear, as is the treatment. The best approach seems to be avoidance of stimulation.

In cold urticaria with persistent wheals, lesions appear in three minutes and last a week or more.[63] Antihistamines are not beneficial *after* exposure, but cyproheptadine can be helpful *prophylactically.*

In cold reflex urticaria, hives occur in the immediate vicinity, rather than at the site of exposure.[21] Symptoms are minor, seasonal, and only an hour or two in duration.

Localized Heat Urticaria

Localized heat urticaria is a rare condition with wheals appearing in the area of heat application or radiant heat exposure within three minutes[84, 170] or after a delay of 1½ to 2 hours.[98] Symptoms are said by some[40, 170] but not others[22, 149] to be reduced by antihistamines or chloroquine.[149, 169] Desensitization is reported to be beneficial.[83]

Cholinergic Urticaria

Cholinergic urticaria is a relatively common physical urticaria with tiny (less than 3 mm) wheals surrounded by a large, prominent flare reaction; this is so characteristic that its appearance is almost diagnostic. Apparently the release of acetylcholine upon stimulation of sweat glands is followed by a histamine release, and this may even cause a rise in the blood histamine level and a fall in FEV_1.[146] The process can be reproduced by intracutaneous injection of methyl acetylcholine, nicotinic acid tartrate, carbamoyl choline chloride, and even saline on occasion, but the best method of reproducing the disease is probably by inducing sweating with exercise.[18] Passive transfer studies have been positive, and this is apparently a hypersensitivity reaction.[162] Treatment with hydroxyzine seems to be helpful.[108] Other treatments include aborting episodes by application of cold water or ice following sweat-inducing stimuli, tolerance (of a day or so) following an episode induced by a hot bath,[108] ultraviolet light,[32] and hypnosis.[133] Although unreported, some dermatologists use tricyclic antidepressants (doxepin, amitriptyline) in resistant cases, but this practice has not been established in a controlled study.

Aquagenic Urticaria

In this rare condition, wheals begin a few minutes to perhaps 30 minutes following exposure to water. This could be a contact urticaria caused by a component of the surface lipid layer. Coating of the skin with an inert oil seems to be protective.[137] Apparently there is a cholinergic component and histamine release,[138] and one patient improved with cyproheptadine.[154]

Vibratory Angioedema and Decompression Urticaria

Angioedema starting some five minutes after stimulation such as massage and vibration and lasting up to an hour has been reported to be inherited as an autosomal dominant trait.[116] In one case, the antihistamine mebhydrolin, 50 mg before exertion, was helpful, but addition of cimetidine diminished the beneficial effect.[46] In decompression urticaria, transient urticaria follows application and removal of atmospheric pressure,[47] and no treatment should be necessary.

Contact Urticaria

Cutaneous signs of contact urticaria vary from atypical burning and irritation to localized or generalized wheal and flare reaction or even a systemic reaction. Therefore, contact urticaria must first be perceived as urticarial and caused by a contactant. Then it can be categorized as immunologic or nonimmunologic by the history followed by appropriate skin testing. Standard testing procedures to confirm the diagnosis have been described recently.[79, 93, 158]

The history is important because it is virtually impossible to test a patient to everything that could cause contact urticaria. Allergic reactions may be followed by extracutaneous manifestations such as rhinitis and conjunctivitis, generalized urticaria, asthmatic symptoms, or even anaphylactoid reactions.[158]

Antihistamines given before exposure to the test substance generally do not reliably prevent positive reactions, but this may at least partially depend upon the test substance.[28, 79, 91, 111, 139] Therefore, the best treatment would seem to be recognition and avoidance of the causative agent.

SUMMARY

Urticaria represents a wide variety of conditions characterized by urticarial papules, wheals, and angioedema. The number of potential causes of urticaria is legion, but a diligent search by careful history and examination is indicated. Laboratory testing depends upon the specific situation, but routine screening examinations are not cost effective. Histamine from mast cells plays an important role in urticaria. Multiple factors, such as aspirin and other nonsteroidal anti-inflammatory agents, direct histamine-releasing agents (including benzoates), tartrazine and other azo dyes, and perhaps blockers of beta^2-adrenergic activity and H_2 receptors, adversely influence histamine release either directly or indirectly. Vasodilatation is also detrimental. Treatment of both acute and chronic urticaria necessitates removal of the patient from aggravating factors as well as the cause of the outbreak (if one can be found), along with effective antihistaminic agents and perhaps beta$_2$-adrenergic agonists. Treatment of specific entities within the urticarial group is briefly outlined in this article.

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