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Chronic urticaria: Pathogenesis and treatment

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Patients previously designated as having chronic idiopathic urticaria are now divided into 2 groups: 40% to 50% with chronic autoimmune urticaria, and the remainder with chronic idiopathic urticaria. Patients in both groups may have concomitant angioedema (approximately 40%). The autoimmune subgroup has an association with antithyroid antibodies and is caused by IgG antibody to the α subunit of the IgE receptor (35% to 40%), usually reactive with unoccupied IgE receptors, or IgG antibody to IgE (5% to 10%). Complement activation augments histamine secretion by release of C5a. The IgG subclasses that appear to be pathogenic are IgG₁, IgG₃, and, to a lesser degree, IgG₄, but not IgG₂. Histology of chronic urticaria (both subtypes) reveals a perivascular non-necrotizing infiltrate of CD4⁺ lymphocytes consisting of a mixture of T_H1 and T_H2 subtypes, plus monocytes, neutrophils, eosinophils, and basophils. These cells are recruited as a result of interactions with C5a, cell priming cytokines, chemokines, and adhesion molecules. Suggested therapy for patients with severe disease involves the use of high-dose hydroxyzine or diphenhydramine when nonsedating antihistamines are ineffective, supplemented by H-2 antagonists and leukotriene antagonists. The most severe patient may require protracted treatment with low-dose alternate-day steroid or cyclosporine. Cyclosporine can be steroid-sparing when side effects are encountered or when use of steroids is relatively contraindicated. Careful monitoring of blood pressure, BUN, creatinine, and urinalysis is required. (*J Allergy Clin Immunol* 2004;114:465-74.)

Key words: Chronic urticaria, skin, anaphylaxis, hives, autoimmune

The traditional definition of chronic urticaria is the presence of hives for more than 6 weeks,¹ and it is usually assumed that hives are present most days of the week. The

physically induced urticarias, such as dermatographism, cold urticaria, and cholinergic urticaria, are commonly included in this nonrestrictive definition, but this article will only consider entities that are now considered to be either chronic autoimmune urticaria or chronic idiopathic urticaria. Patients with either of these latter forms of chronic urticaria do not have IgE-mediated hypersensitivity to exogenous allergens as the cause of symptoms and are distinct from the aforementioned physically induced urticarias. Another distinction is pathogenic. Physically induced hives, with the sole exception of delayed-pressure urticaria, have no late-phase response after the initiating urticarial response and therefore have hives lasting no more than 2 hours, whereas individual lesions in patients with chronic autoimmune urticaria or chronic idiopathic urticaria last 4 to 36 hours. The exception, delayed-pressure urticaria, is often seen accompanying either of the 2 types of chronic urticaria, but the diagnosis of chronic urticaria requires the presence of spontaneously occurring hives that are not attributable to a pressure stimulus. It is also recognized that about 40% of patients with either chronic autoimmune or chronic idiopathic urticaria have associated angioedema, most typically involving the face (cheeks and periorbital area), lips, tongue, pharynx, and extremities.² Genital swelling is occasionally seen but is more common in men with idiopathic angioedema, whereas laryngeal swelling is seen with C1 inhibitor deficiency, angioedema caused by angiotensin-converting enzyme inhibitors, or frank anaphylaxis.

There is a large set of literature dealing with possible causes of chronic urticaria and angioedema that include psychophysiologic reactions, food allergies, adverse reactions to food additives, cutaneous fungal infections (id reactions), and, most recently, hives as a consequence of infection with *Helicobacter pylori*.³⁻⁵ Gradually, all of these have been dispelled as myth or erroneous associations, with the exception of *H pylori*; however, there are data suggesting that the association is a chance occurrence and not a cause-and-effect relationship.⁶⁻⁹ My own view is that none of these are common as a cause of chronic hives or swelling. However, as long as a large idiopathic group exists, ideas may come and go until clinical or basic studies that are reproducible lead to a consensus regarding cause, as has emerged for the "autoimmune" subgroup.

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TABLE I. Relationship of antithyroid antibodies to anti-IgE receptor antibody

	Antithyroid, positive	Antithyroid, negative	Total
Histamine release, positive	40 (27.7%)	104 (72.3%)	144
Histamine release, negative	15 (10.9%)	123 (89.1%)	138
Totals	55	227	282

$P < .001$, χ^2 test.

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AUTOIMMUNITY AND CHRONIC URTICARIA: HISTORICAL OBSERVATIONS

The first suggestion that patients with chronic urticaria and angioedema might have an autoimmune diathesis was the observation that there is an increased incidence of antithyroid antibodies in such patients relative to the incidence in the population at large.¹⁰ These include anti-microsomal (peroxidase) and anti-thyroglobulin antibodies, as are associated with Hashimoto thyroiditis.¹¹ Patients might have clinical hypothyroidism, and a small number might have hyperthyroidism if thyroid inflammation is at an early stage at which thyroid hormone leaks out, whereas most patients are classified as euthyroid (subclinical). The incidence of anti-thyroid antibodies in chronic urticaria, as reported in the literature, varies between 15% and 24%,^{12,13} but the most recent data are closer to the latter figure and demonstrate segregation of anti-thyroid antibodies with chronic autoimmune urticaria rather than chronic idiopathic urticaria (Table I). The association is, however, not absolute. The incidence in the autoimmune subgroup was 27%, that in the chronic idiopathic urticaria subgroup was 11%, and that in the population at large was 7% to 8%. Gruber et al¹⁴ considered the possibility that patients might have circulating anti-IgE antibodies that are functional and did indeed find these in about 5% to 10% of patients. Grattan et al^{15,16} sought antibodies reactive with skin mast cells by performing an autologous skin test and found a 30% incidence of positive reactions in patients with chronic urticaria. There were only rare positive reactions in healthy control subjects or patients with other forms of urticaria. Subsequently, this level of positivity was shown by Hide et al¹⁷ to be due to an IgG antibody reactive with the α subunit of the IgE receptor; in addition a 5% to 10% incidence of functional anti-IgE antibodies was confirmed.^{17,18} Augmented histamine release observed when IgE was stripped from the basophils substantiated the presence of antireceptor antibody, whereas a prominent decrease of histamine release on stripping off the IgE indicated the presence of anti-IgE. The antibody was of the IgG class, with only rare instances of IgM antibody; this is depicted in Fig 1. The anti-receptor antibody interacts with unoccupied IgE receptors in most instances, although some exceptions do exist. This was shown by means of inhibition of basophil histamine release stimulated by sera

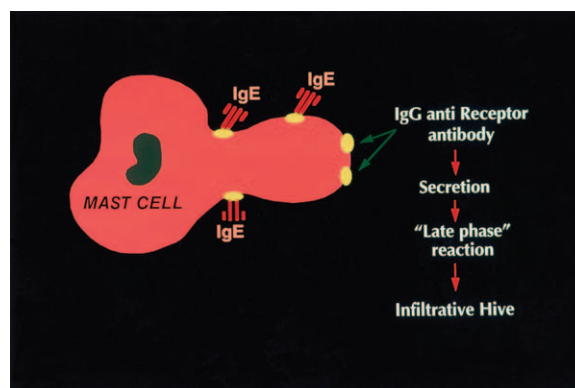


FIG 1. Diagram of the activation of cutaneous mast cells by IgG antibody directed to the IgE receptor.

from patients with chronic urticaria if the basophils were first preincubated with an IgE myeloma protein (Fig 2). Thus IgE antibody or IgG anti- α might bind to the same epitope on the α chain, or bound IgE sterically interferes with the ability of the autoantibody to interact with the α chain.

FUNCTIONAL ASSAYS OF ANTI-IgE RECEPTORS

Assays for anti-IgE receptor antibody have included *in vivo* methods and *in vitro* assays. The autologous skin test,^{2,15} as noted above, provided one of the first clues that a subset of patients with chronic urticaria have an autoimmune disorder. Basophils are frequently used as an *in vitro* surrogate for mast cells, and secretion of histamine as a result of incubation with patient sera or purified IgG was readily demonstrated¹⁹⁻²¹ but was not observed if the source of basophils was from a nonreleaser (ie, basophils with an abnormality in the signal transduction molecules lyn or syc, which are unresponsive to signals through the IgE receptor but are normally responsive to other secreteagogues, such as cytokines; Fig 3). The incidence of a positive assay result was generally higher than that observed with the autologous skin tests with reported values of 35% to 50%.^{19,21,22} Absorption of sera, with cloned α subunit, decreased the percentage of histamine release as the amount of added α subunit was increased.²³ The assay could be made more sensitive by preincubating basophils with IL-3,²⁴ although the percentage of positive reactions was not significantly affected (Fig 4). Release of leukotriene C4 and IL-4, along with histamine, was also demonstrable.^{25,26} Although more cumbersome, activation of cutaneous mast cells could also be performed *in vitro* by using either thin skin slices²⁷ or partially purified mast cells derived from foreskin samples.²⁸

BINDING ASSAYS FOR ANTI-RECEPTOR ANTIBODY

Attempts to quantitate IgG antibody to the α subunit have, in general, been unsuccessful. Initial attempts to

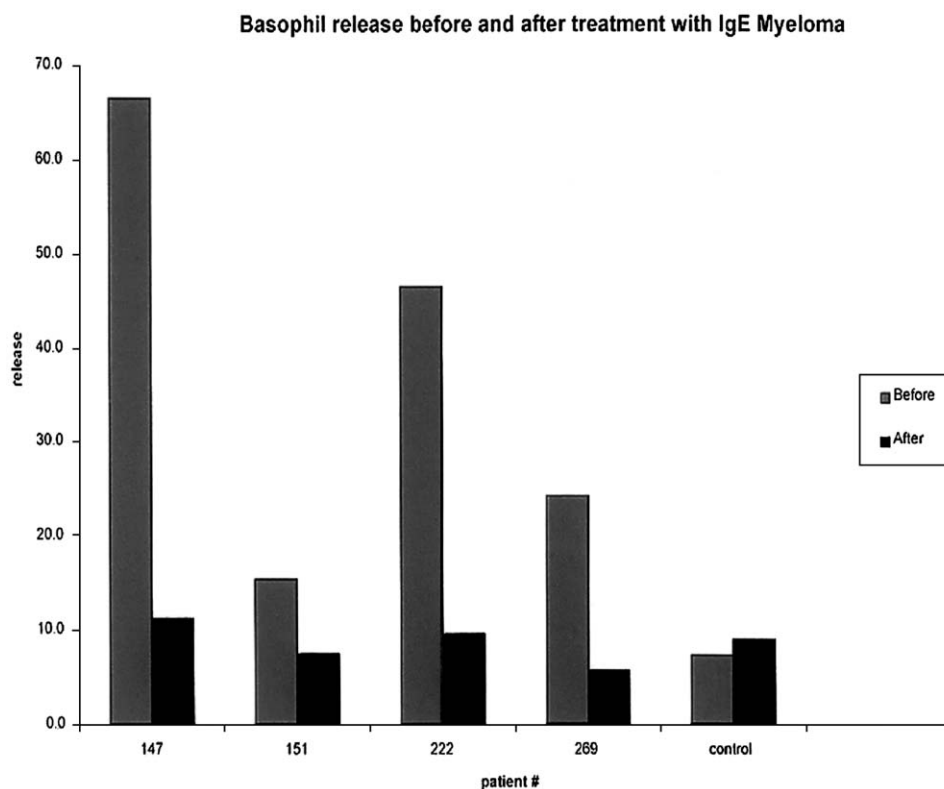


FIG 2. Inhibition of histamine release by saturation of IgE receptors through incubation with an IgE myeloma protein.

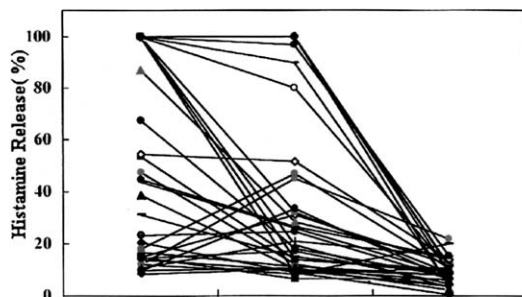
demonstrate the presence of the antibody by means of immunoblotting^{22,29} have not proved useful because positive reactions might be seen in other autoimmune disorders²⁹ or occasionally with sera²² from subjects with no history of urticaria. In addition, studies of the relationship of a positive immunoblot result with histamine release did not yield a significant correlation²³; sera with a positive blot result but negative release were frequently seen. However, sera with positive histamine release and a negative blot result did have demonstrable IgG anti- α because absorption of such sera with the α subunit inhibited histamine release. Thus lack of sensitivity of the immunoblot explained part of the discrepancy, but the cause of the false-positive blot results was not apparent. Recently, a series of publications have demonstrated that normal serum has natural antibody to the α subunit of the IgE receptor, which has germline variable region sequences and is primarily IgM.^{30,31} Such antibodies can be functional but appear to require stripping of IgE from donor basophils. Evidence to suggest cross-reactivity of anti- α antibody with tetanus toxoid was reported,³² which implied immunization as a course of such antibodies; however, we have been unable to absorb sera with tetanus toxoid and diminish histamine release (unpublished observations), and if such antibodies are part of our innate repertoire, no external stimulus is needed to explain their presence. But some unknown stimulus or abnormal control mechanism might lead to pathogenic IgG antibody, such as we have seen.

Subclass analysis of the pathogenic IgG has been helpful in further delineating the relationship (or lack thereof) of binding assays versus functional methods. An early report suggested that much of the anti-receptor antibody exists within the IgG1 and IgG3 subclasses, but these data were based on immunoblot analysis.²⁹ Thus we have begun to purify IgG subclasses from the sera of patients with chronic urticaria to determine which have functional anti-receptor antibody. Thus far we have isolated IgG2 antibody from 9 patients with chronic urticaria, and all had negative results for histamine release, irrespective of whether a positive IgG2 anti- α antibody immunoblot result is seen. Much of the histamine release appears to be due to the IgG1 and IgG3, as well as IgG4, subclasses (Soundararajan, Joseph, and Kaplan, manuscript in preparation); however, this is demonstrable by histamine release assay of IgG subclasses isolated by means of affinity chromatography and is not reliably predicted with any binding method available to date. Correlation of histamine release with IgG subclass levels of antibody directed specifically to the α receptor of the IgE receptor will be required before development of a binding assay for clinical use, and the assay will need to be subclass specific.

THE ROLE OF COMPLEMENT

The notion that complement might contribute to the histamine release observed with sera from patients with

A



B

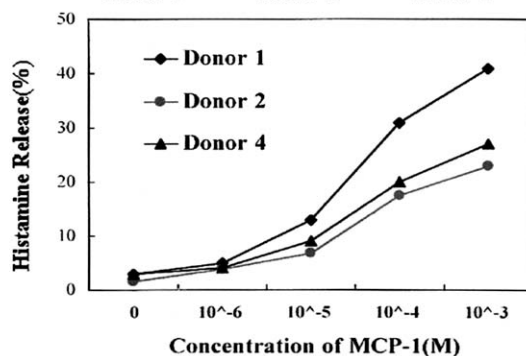


FIG 3. A, Variability in ability to release histamine from basophils from 3 different donors (donor 1, donor 2, and donor 4). Basophils were incubated with 35 sera from patients with chronic urticaria, and the percentage of histamine release was determined. **B,** Percentages of histamine release from basophils from 3 different donors (donor 1, donor 2, and donor 4) stimulated with different concentrations of monocyte chemoattractant protein 1 (10^{-6} , 10^{-5} , 10^{-4} , and 10^{-3} mol/L). Reprinted from *The Journal of Allergy and Clinical Immunology*, Vol 107, Kikuchi and Kaplan, Pages 1056-62, Copyright 2001, with permission from the American Academy of Allergy, Asthma and Immunology.

chronic urticaria was suggested by studies in which complement depletion or inactivation appeared to diminish histamine release.^{20,29} A series of reports by Ferrer et al²⁸ and Kikuchi and Kaplan^{23,33} then documented not only a role for complement but also more specifically activation of the classical pathway and generation of C5a. First, we demonstrated that the addition of purified patient IgG to normal serum (as a source of complement) but not sera deficient in C2 or C5 augmented cutaneous mast cell histamine release (Fig 5).²⁸ This was confirmed with basophils.^{23,33} As shown in Fig 6, we could reconstitute C5-deficient serum with purified C5²³ to recover the augmentation of histamine release provided by serum (Fig 7). Then we demonstrated inhibition of the complement contribution to histamine release by using an antibody to the C5a receptor.³³ It is not clear why the presence of a functional anti-IgE receptor would cause symptoms limited to the skin, but among the differences between pulmonary and cutaneous mast cells is the absence of C5a receptors on lung mast cells. On the other hand, it is also not clear why the IgG2 anti-IgE receptor antibody, which

is often demonstrable by means of immunoblotting, does not activate basophils or cutaneous mast cells because IgG2 anti-FcεRIα should cross-link α subunits, as might any IgG subclass antibody directed to the α subunit. The difference might have to do with antibody affinity or differing α subunit epitopes with which these antibodies might react or nonfunctional binding to α subunit bound to a matrix that might not occur *in vivo*. The geometry of binding is also a factor because the Fc region of 2 adjacent IgG molecules must each be able to bind to one of the globular heads of C1q to initiate complement activation (Fig 8). It is theoretically possible to have binding of IgG to the IgE receptor in the absence of cross-linking (eg, the receptors are too far apart) and still observe histamine release if the 2 Fc regions are sufficiently close together to activate C1. If receptors are sparse, the antibody can bind without activation of the cells or of complement, whereas receptors saturated with IgE might preclude binding.

THE CELLULAR INFILTRATE

Mast cell degranulation certainly initiates the inflammatory process in autoimmune chronic urticaria and is assumed to also do so in idiopathic chronic urticaria. However, no alternative mechanism for mast cell degranulation in the idiopathic groups has been suggested to date. Yet the histology of the 2 groups is virtually indistinguishable and differs only in minor ways. There is, however, considerable heterogeneity evident when individual patients are compared. Common to all biopsy specimens is a perivascular infiltrate that surrounds small venules within the superficial and deep venular plexus, with a prominence of CD4⁺ T lymphocytes and monocytes and virtually no B cells.^{34,35} Granulocytes are quite variable but are plentiful if the lesion undergoes biopsy early in its development. Neutrophils and eosinophils are both present,^{36,37} although the degree of eosinophil accumulation varies greatly.³⁵ Even when eosinophils are not evident, major basic protein can be identified within lesions (in at least two thirds of patients), which most likely represents evidence of prior eosinophil degranulation.³⁸ The presence of basophils has also been recently demonstrated by using an antibody (BB1) that is specific for this cell type.³⁷ Thus the infiltrate resembles that of a late-phase reaction, as suggested previously,³⁹ although the percentage of each cell type differs, with neutrophils and monocytes being relatively more prominent in urticaria. The recruitment of these cells requires release of cytokines and chemotactic factors active on each cell type and activation and recruitment of adhesion molecules on the migrating cell, as well as the endothelial cell. This combination of integrins and selectins mediates various aspects of cell migration, including rolling along the endothelial cell surface, firm adhesion, and then transmigration. Endothelial cell activation is suggested by the presence of intercellular adhesion molecule 1 and E-selectin in biopsy specimens of urticarial lesions.⁴⁰ Sources of chemokines include the



FIG 4. Basophil activation before and after priming of cells with IL-3. The cells are then incubated with sera from patients with chronic urticaria that were known to stimulate histamine release. Reprinted from Ferrer M, Luquin E, Kaplan AP. IL3 effect on basophils histamine release upon stimulation with chronic urticaria sera. *Allergy* 2003 Aug;58(8):802-7. Published by Blackwell Publishing Ltd.

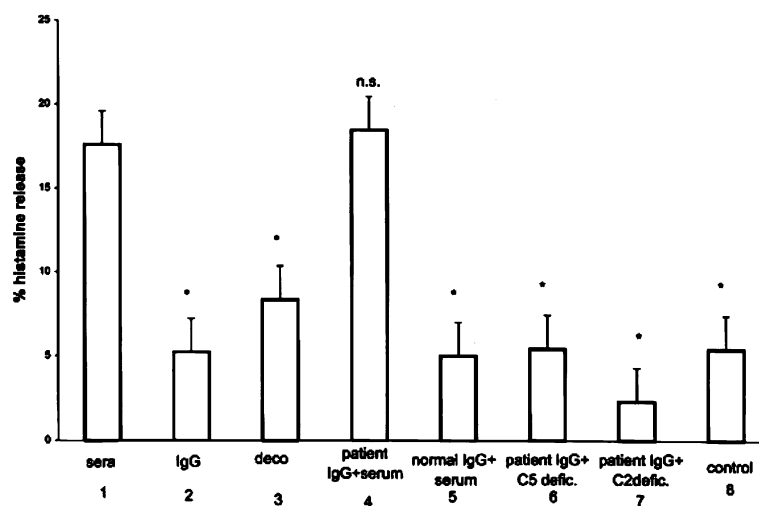


FIG 5. Average of mast cell histamine release on incubation of cells with patient sera or isolated patient IgG plus sera. Seventy-five microliters of a cell suspension containing 2×10^5 mast cells was incubated for 20 minutes at 37°C with 75 μ L of patient or control serum, 75 μ L of decompartmented patient serum (for 1 hour at 56°C), 75 μ L of 1 to 10 mg/mL protein G–eluted IgG, 15 μ L of purified IgG plus 60 μ L of pooled normal serum, 15 μ L of pure IgG plus 60 μ L of C5- or C2-deficient serum, or 75 μ L of buffer. Results are expressed as a percentage of histamine release from 2 cell-suspension replicates. Cells were boiled to determine total histamine content. Significant differences ($P < .05$ as determined with the Student *t* test) for paired samples, each of which was compared with the histamine release for patient sera (far left bar), are indicated by asterisks. Each bar represents an average of histamine release by 5 different patient sera, each of which was assayed 5 times in duplicate ($n = 50$). Reprinted from *The Journal of Allergy and Clinical Immunology*, Vol 104, Ferrer et al, Pages 169-72, Copyright 1999, with permission from the American Academy of Allergy, Asthma and Immunology.

mast cell and the activated endothelial cell; the latter cells are stimulated not only by cytokines or monokines, such as IL-4, IL-1, and TNF- α , but also by the vasoactive factors—eg, histamine and leukotrienes released from activated mast cells.⁴¹ Complement activation and the release of C5a results not only in augmented mast cell (and basophil) histamine release, but also C5a is chemotactic for neutrophils, eosinophils, and monocytes, which is one

of the factors that would distinguish this lesion from a typical allergen-induced cutaneous late-phase reaction. The particular chemokines released in chronic urticaria have not been studied. The presence of increased plasma IL-4 levels²⁵ in patients with chronic urticaria provides indirect evidence of lymphocyte activation, basophil activation, or both, and isolated CD4⁺ lymphocytes of patients were shown to secrete greater amounts of both

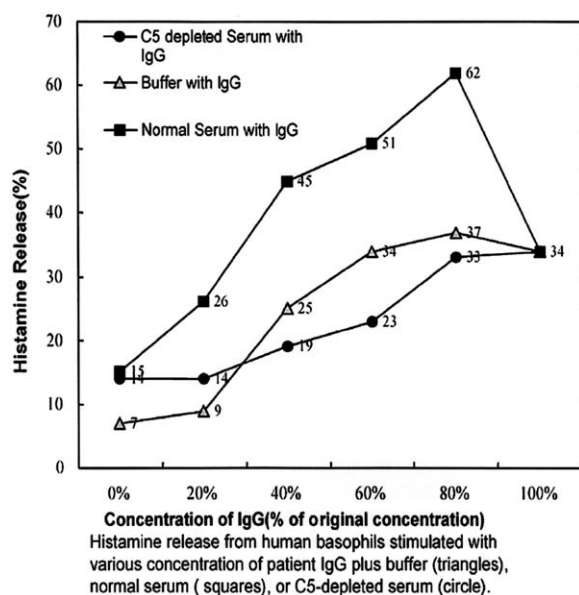


FIG 6. Histamine release (percentage) from human basophils stimulated with various concentrations of patient IgG plus either buffer (open triangles), normal serum (filled squares), or C5-depleted serum (filled circles). Reprinted from *The Journal of Allergy and Clinical Immunology*, Vol 109, Kikuchi and Kaplan, Pages 114-8, Copyright 2002, with permission from the American Academy of Allergy, Asthma and Immunology.

IL-4 and IFN- γ compared with that seen in healthy control subjects on stimulation with phorbol myristate acetate.

A direct comparison between cutaneous late-phase reactions and the histology of chronic urticaria revealed that infiltrating cells had characteristics of both T_H1 and T_H2 cells (Fig 9), with production of IFN- γ by the former cells and IL-4 and IL-5 by the latter.⁴² Alternatively, this might represent activated T_H0 cells (ie, activated CD4⁺ lymphocytes that have not differentiated to T_H1 or T_H2 cells). When the histology of autoimmune and idiopathic chronic urticaria was compared,³⁷ the autoimmune subgroup had more prominence of granulocytes within the infiltrate, whereas other infiltrating cells were quite similar (Table II), with a small increment in cytokine levels in the autoimmune group and greater tryptase positivity (? less degranulation) in the autoantibody-negative group. The patients with autoimmune chronic urticaria generally had more severe symptoms than those with idiopathic chronic urticaria.⁴³

The basophils of patients with chronic urticaria have been shown to be hyporesponsive to anti-IgE, an observation made by Kern and Lichtenstein⁴⁴ long before there were any clues to the pathogenesis of this disorder. These findings were confirmed⁴⁵ and appeared to be associated with basopenia⁴⁶ and to segregate with the autoimmune subgroup. The interpretation is that there is *in vivo* desensitization of basophils in the presence of circulating anti-IgE receptor. However, we have found a paradoxical result when the isolated basophils of patients with chronic urticaria were activated and compared with the basophils of healthy control subjects. Although the

basophils of the patients with urticaria were clearly less responsive to anti-IgE, they demonstrated augmented histamine release when incubated with the sera of patients with chronic urticaria, and it did not matter whether the sera were taken from other patients or was their own (Ferrer and Kaplan, unpublished observations). This augmented responsiveness of basophils was evident when basophils were isolated from patients with idiopathic chronic urticaria, as well as from those with autoimmune chronic urticaria, and might represent a cellular abnormality of basophils present in patients with all types of chronic urticaria, irrespective of whether the autoantibody is present and whether hyporesponsiveness to anti-IgE is present. The nature of this augmented reactivity and the nature of the serum factor that appears to stimulate these cells is unknown. Other data suggesting an underlying abnormality in signal transduction in patients with chronic urticaria include increased expression of the p21ras proto-oncogene and low expression of the regulatory protein "son of sevenless" (hSOS1).⁴⁷

TREATMENT CONSIDERATIONS

A review of the treatment of chronic urticaria has been recently published,⁴⁸ including a critical assessment of approaches that are evidence based. The mainstay of initial treatment is the use of antihistaminic agents active at the H1 receptor. Alternate-day steroids may be used for patients with severe disease,^{1,48} and immunosuppressive agents, such as cyclosporine, can also be used for patients with severe disease.⁴⁹⁻⁵¹ Cyclosporine also inhibits basophil and mast cell degranulation, which might account for its effectiveness.^{52,53} Medications that might also be useful but are adjunctive agents include H2 receptor antagonists and leukotriene antagonists. There is literature regarding the use of agents such as hydroxychloroquine, dapsone, sulfasalazine, and colchicine in chronic urticaria, but no large controlled studies of these agents are available. Some of these might be useful for cutaneous vasculitis with urticaria (urticarial vasculitis), but this author has had little success with any of these in the treatment of chronic urticaria. However, it should be noted that hydroxychloroquine is particularly effective for the treatment of the hypocomplementemic urticarial vasculitis syndrome.⁵⁴

The use of antihistamines in chronic urticaria is quite different from their use in allergic rhinitis. I will address this issue using treatment of severe dermatographism as an example because it is mediated primarily by histamine, and there is no associated late-phase response. Thus one would think that any of the nonsedating antihistaminic agents would suffice. However, it is common experience that patients presenting with severe symptoms might already be taking one of them regularly. Increasing the dose (eg, fexofenadine 180 mg in the morning plus cetirizine, 10 mg twice daily) might provide further relief, but some patients remain significantly symptomatic, with a clear dermatographic response still present. My next step is to use either

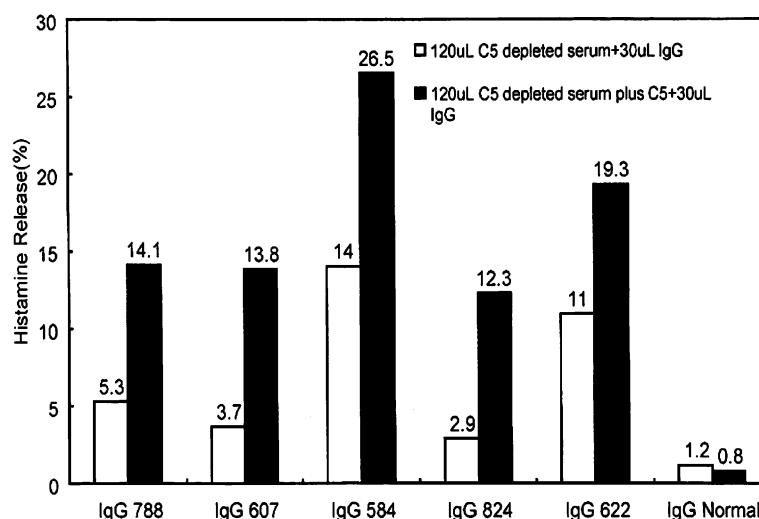


FIG 7. Histamine release (percentage) observed on incubation of 5 patients' IgG or normal IgG with C5-depleted serum (*open bars*) or C5-depleted serum reconstituted with C5 (*filled bar*). Reprinted from *The Journal of Allergy and Clinical Immunology*, Vol 109, Kikuchi and Kaplan, Pages 114-8, Copyright 2002, with permission from the American Academy of Allergy, Asthma and Immunology.

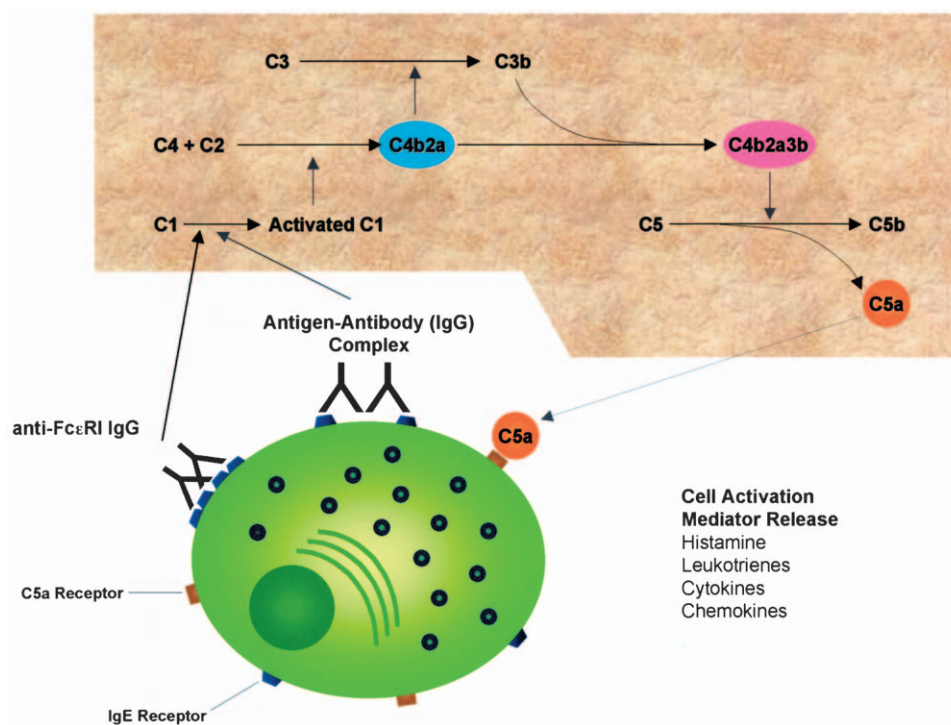


FIG 8. Diagrammatic representation of mast cell activation by cross-linking the IgE receptor, followed by complement activation and release of C5a.

hydroxyzine or diphenhydramine at 50 mg 4 times daily. The typical result is relief of symptoms within 72 hours, and scratching the skin yields no wheal, but a prominent flare always persists. How could that happen if all the histamine H1 receptors had been blocked? Might those agents have additional activities evident at the higher dosage?

Could the histamine released intracutaneously be so high that H1 receptors are activated rather than inactivated?

One concern regarding the use of antihistaminic agents in this dose range is sedation and impairment of performance⁵⁵; when tested acutely, diphenhydramine can be as impairing as alcohol.⁵⁶ Nevertheless, the

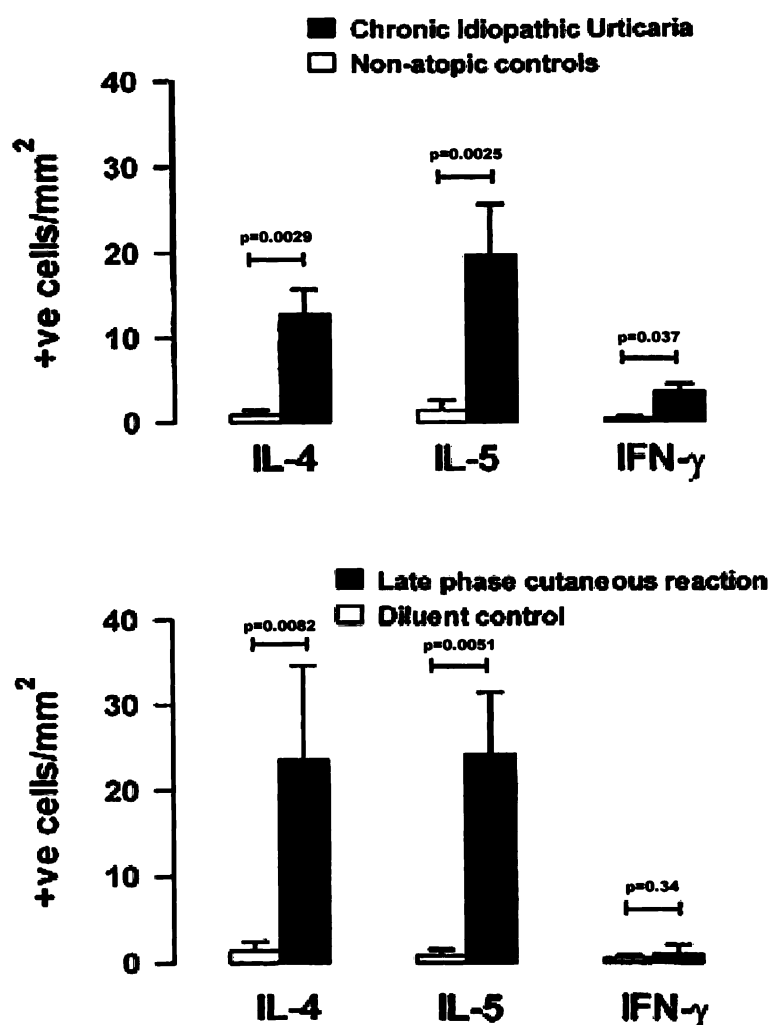


FIG 9. Comparison of tissue distribution of cytokines typical of T_H1 and T_H2 responses in chronic urticaria versus an allergic late-phase reaction. The numbers of cells expressing mRNA for IL-4, IL-5, and IFN- γ in skin biopsy specimens from healthy nonatopic control subjects (*open columns*, $n = 6$; *top*) and patients with chronic idiopathic urticaria (*filled columns*, $n = 13$; *top*) and diluent challenge sites (*open columns*, $n = 6$; *bottom*) and allergen-induced skin late-phase reaction sites (*filled columns*, $n = 6$; *bottom*) are shown. The results are expressed as the numbers of positive cells per square milliliter of biopsy specimen. The differences between patients with chronic idiopathic urticaria and healthy control subjects or allergen-challenged skin late-phase reaction sites and diluent-challenged control sites were analyzed by means of the Mann-Whitney U test. Reprinted from *The Journal of Allergy and Clinical Immunology*, Vol 109, Ying et al, Pages 698-799, Copyright 2002, with permission from the American Academy of Allergy, Asthma and Immunology.

TABLE II. Comparison of the numbers of inflammatory cells and mRNA-positive cells in skin urticarial lesions between patients with and without autoantibody

Subjects	Eosinophils	BB1	CD3	CD4	CD8	CD25	Tryptase	CD68	Elastase	IL-4	IL-5	IFN- γ
Auto	11.5	3.4	40.0	32.2	18.8	10.2	21.2	57.4	62.6	13.6	16.9	3.1
Antibody positive	0.0-49.3	0.0-28.1	26.6-94.6	16.2-92.1	13.0-40.5	7.6-21.9	17.4-59.0	33.6-70.5	30.8-101.6	3.3-19.9	4.4-25.5	0.0-7.7
Auto	10.5	2.5	77.0	32.7	21.2	11.9	40.8	66.6	47.9	5.5	12.3	2.2
Antibody negative	0.0-45.3	0.9-36.8	38.8-164.2	11.8-121.1	1.1-37.3	5.7-37.4	23.1-56.4	31.9-76.6	15.8-121.3	0.7-40.1	1.7-77.4	0.0-9.8

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perception of sedation wears off in 1 week, auto accidents have not occurred in those I treat, and no gross abnormality is discerned when interviewing or observing such patients. Sedation is indeed variable and inconsistent, which has been recently emphasized in a meta-analysis of all the available studies.⁵⁷ No studies have been done after sustained use in this fashion to determine actual degree of functional impairment, and in one study statistically significant impairment on day 1 observed with a single 50-mg dose was no longer statistically significant on day 4 when the dose was given daily.⁵⁵ The point is that use of the aforementioned doses in chronic urticaria, which has a more complex pathogenesis than dermatographism, particularly when it is severe and associated with angioedema, is warranted if there is relief of pruritis and lessening of the hives, swelling, and disability,⁵⁸ and this is certainly true if they are steroid sparing.

Chronic urticaria differs from dermatographism because hives can last all day instead of 1 to 2 hours, there is a prominent late-phase reaction, angioedema is far more commonly seen, and complement has a role. Thus one should not be surprised that antihistaminic agents at any dose might be insufficient to treat the disorder. It is like treating asthma without being able to use an inhaled corticosteroid. In fact, the efficacy of low-dose, alternate-day steroids in chronic urticaria^{1,48} attests to the importance of the cellular infiltrate because steroids do not affect cutaneous mast cell degranulation nor do they affect complement activation. Cyclosporine, however, is an agent that has been shown to be effective in a controlled study.⁵¹ We concur and now use it in patients whose steroid requirement is prohibitive or who have significant steroid side effects on presentation or as an alternative to steroids, especially in patients who have diabetes, glaucoma, osteoporosis, ulcer disease, or obesity, circumstances in which steroid use is relatively contraindicated. In such patients we perform blood pressure, blood urea nitrogen, and creatinine measurement and urinalysis regularly. Nevertheless, I wish to emphasize that maximizing antihistaminic agents as noted above plus an H₂ receptor antagonist and a leukotriene antagonist allows us to wean many patients off corticosteroids when the dosage of these agents had not been maximized (ie, steroids have been used as if the attendant side effects of steroid use are preferred to the potential sedation of antihistamines).

Clearly the treatment of chronic urticaria will be facilitated when it becomes more specifically tied to pathogenic mechanisms. Examples would be use of immunomodulators to downregulate the IgE receptor or to block the formation of C5a or perhaps to interrupt the development of the cellular infiltrate by using agents that are reactive with critical cytokines, chemokines, or adhesion molecules.

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