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STATE-OF-THE-ART REVIEW

Pathogenesis of chronic urticaria

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Clinical & Experimental Allergy

Summary

Chronic urticaria is defined as the presence of urticaria (hives) for at least 6 weeks with the assumption that it occurs daily or close to it. If we eliminate physical urticarias and urticarial vasculitis from consideration, the remainder can be divided into autoimmune chronic urticaria (45%) and idiopathic chronic urticaria (55%). The autoimmune subgroup is associated with the IgG anti-IgE receptor α subunit in 35–40% of patients and IgG anti-IgE in an additional 5–10%. These autoantibodies have been shown to activate blood basophils and cutaneous mast cells *in vitro* with augmentation of basophil activation by complement and release of C5a, in particular. Binding methods (immunoblot and ELISA) yield positives in many autoimmune diseases as well as occasional normal subjects or patients with other forms of urticaria but most such sera are non-functional. Activation of basophils or mast cells causing histamine release is quite specific for chronic urticaria and defines the autoimmune subgroup. Although pathogenicity is not formally proven, the antibodies cause wealing upon intradermal injection, and removal of the autoantibody leads to remission. A cellular infiltrate is seen to be characterized by mast cell degranulation and infiltration of $CD4^+$ T lymphocytes, monocytes, neutrophils, eosinophils, and basophils. The intensity of the infiltrate and clinical severity of the disease (including accompanying angio-oedema) is more severe in the autoimmune subpopulation. This latter group also has a higher evidence of human leucocyte antigen DR alleles associated with autoimmunity and a 25% incidence of antithyroid antibodies with diagnosed hypothyroidism in some. Hypo-responsiveness of patients' basophils to anti-IgE and hyperresponsiveness to serum defines another subpopulation (at least 50%) that overlaps the idiopathic and autoimmune subgroups. Hypo-responsiveness to anti-IgE has been shown to be associated with elevated levels of cytoplasmic phosphatases that inhibit degranulation. Reversal of the abnormality is seen with disease remission. Further work will be needed to distinguish whether this is a cause or a consequence of persistent urticaria and to further assess the relationship (or lack thereof) of altered responsiveness (decreased or increased) with the presence or absence of activating autoantibodies.

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Introduction

Chronic urticaria (with accompanying angio-oedema in 40% of patients) is defined as having urticaria for over 6 weeks with symptoms present daily or close to it [1, 2]. There is no evidence of an exogenous allergen as the cause of the disorder, and for the purposes of this discussion, physical urticarias such as dermatographism or cholinergic urticaria and urticarial vasculitis are excluded.

Pathogenic mechanisms that are responsible for the development of chronic urticaria have been elucidated during the past 20 years. Evidence of an autoimmune aetiology in approximately 45% of patients has been presented [3–7] and remains an area of active investigation. The aetiology in the remaining 55% of patients is unknown and this group remains 'idiopathic'. A very different approach focuses on basophil responsiveness and signal transduction with abnormal responsiveness noted in at least half the patients [8–12]. This abnormality does not necessarily correlate with the presence of autoimmunity, and yet abnormal responsiveness has been observed to normalize as patients' symptoms remit [13]. In this manuscript, the data upon which these observations are based will be reviewed and discussed.

Autoimmunity and antithyroid antibodies

We know that the weals of chronic urticaria are in part due to the release of histamine and other vasoactive substances from dermal mast cells [14]. The suggestion that chronic urticaria might be the result of the action of circulating histamine-releasing factors is not new and has been proposed by earlier authors. In the early 1960s, Rorsman [15] observed a paucity of circulating peripheral blood basophils in urticaria, and proposed that 'antigen–antibody reactions . . . bring about degranulation of basophil leucocytes'.

Indirect evidence that chronic 'idiopathic' urticaria might have an autoimmune basis has been known for many years. In 1983, Leznoff et al. reported an association between thyroid autoimmunity and chronic idiopathic urticaria, and in 1989 Leznoff proposed a 'syndrome' of autoimmune thyroid disease and chronic urticaria and angio-oedema [16, 17] with thyroid autoantibodies identified in 15% of patients. Symptomatic thyroid disease, most frequently Hashimoto's thyroiditis, may be seen, while Graves' Disease is much less common [18]. Published figures for the incidence of thyroid autoantibodies in chronic idiopathic urticaria range from 5% to 90%. However, O'Donnell et al. [19] reported that of 182 patients with chronic urticaria, 22 had antithyroid microsomal autoantibodies (12%). Eighteen of these were autologous serum skin test positive, suggesting an association with serum factors mediating histamine release. Thyroid-stimulating hormone plasma levels were elevated in 14 patients, all but one of whom was autologous serum skin test positive. Kikuchi et al. [20]reported an incidence of antimicrosomal antibodies plus antithyroglobulin antibodies in 24% of patients, and the presence of those antibodies was associated with basophil histamine release. The incidence in the patients negative for serum-dependent basophil histamine release was 10% [20] while the reported incidence in the general population is 7%. Nevertheless, most patients with chronic idiopathic urticaria and thyroid autoantibodies are euthyroid. Recently published guidelines [21] recommend that thyroid autoantibody determination and thyroid function testing should be considered, and not performed routinely, except if there is a clinical or a family history pointing towards thyroid dysfunction. Nevertheless, their determination may provide some indirect evidence of an autoimmune aetiology of the process. That treatment of thyroid dysfunction in patients with idiopathic urticaria favourably influences the urticaria is often claimed [19], but remains unproved. It is also worth noting that determinations of the human leucocyte antigen (HLA) class 2 alleles in chronic idiopathic urticaria patients revealed a significantly increased frequency of HLA DRBI*04 (corrected $P = 3.6 \times 10^{-6}$) for patients with evidence of autoimmune chronic urticaria [22], a result consistent with the view that an autoimmune basis underlies this subset of chronic urticaria patients.

Abnormal cellular function

In 1974, Greaves et al. [8] made the observation that basophils of patients with chronic urticaria are hyporesponsive to anti-IgE and soon thereafter Kern and Lichtenstein [9] confirmed that blood basophil suspensions from patients with chronic idiopathic urticaria had diminished basophil-releasing ability with agonists such as anti-IgE. This finding suggested basophil desensitization but its significance was not appreciated. We now know that basophil desensitization, together with a parallel reduction in basophil numbers in chronic urticaria, is due, at least in part, to the action of circulatory histamine-releasing autoantibodies [10]. Recent studies have re-examined this observation, and data have emerged suggesting an abnormality in signal transduction observed in basophils of patients with chronic urticaria. Luquin et al. [11] also reported basophil hypo-responsiveness to anti-IgE (Fig. 1) but paradoxically, hyper-responsiveness, to a serum factor. However, these abnormalities were not confined to those patients with autoantibodies; thus, an intrinsic abnormality in signal transduction might be present. Recently, Vonakis et al. [12] reported hypo-responsiveness in a subpopulation of patients with chronic urticaria (about half) attributed to excessive activity of SHIP that dephosphorylates kinases such as syk and thereby diminishes cell responsiveness. The authors contend that the two basophil subpopulations (normally responsive vs. hypo-responsive) do not correspond to those patients considered to have autoimmune features vs. those who are still considered to be idiopathic. Reversal of hypo-responsiveness was observed with improvement of symptoms or remission, suggesting a relationship of the abnormality observed with the pathogenesis of the urticaria [13]. Because a diminished responsiveness is observed, it seems more likely to represent an abnormality that is a consequence of the urticarial reaction rather than a cause of it. The paradoxical hyper-responsiveness to serum [11] needs to be further characterized in terms of the serum factor that is reactive with basophils as well as the definition of any abnormality of signal transduction with which it might be associated. Hyperresponsive basophils were also

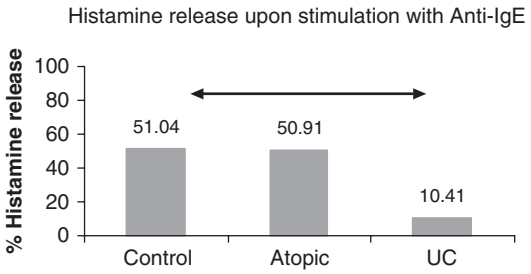

Fig. 1. Percent histamine release upon stimulation of basophils with rabbit anti-human IgE. There is no discernable difference in histamine release of normal control subjects compared with atopics (allergic rhinitis, asthma) while patients with chronic urticaria are hypo-responsive.

observed by Lourenco et al. [23], who demonstrated that basophils of patients with chronic urticaria have increased surface expression of FcεRIα (which correlated with IgE levels) and augmented responsiveness to IL-3, suggesting *in vivo* priming. Yet exogenous addition of IL-3 to patient basophils augments the magnitude of serum-induced histamine release but does not change responder from non-responder basophils [24]. Another abnormality of cellular function reported earlier is abnormal signalling through the P21 Ras pathway in lymphocytes of patients with chronic urticaria. Because there was no other assessment of autoimmune phenomenon in such patients, the abnormality may be present in patients lacking autoantibodies such as anti-IgE or anti-FcεRI.

Evidence for involvement of a circulating histamine-releasing factor

The idea that autoantibodies directed against epitopes expressed by mast cells or basophils could be an important cause of histamine release in urticaria is not a novel concept. In 1988, Gruber et al. [25] reported that some patients with cold urticaria had autoantibodies of the IgG class directed against IgE as determined by an enzyme immunoassay. These antibodies were also found in 5–10% of patients with chronic urticaria. The serum of one cold urticaria patient was shown to release histamine from normal human basophils, and immunoabsorption studies indicated that this activity was located in the IgM anti-IgE fraction of the serum. None of the immunoreactive sera caused an immediate weal and flare reaction upon intradermal injection. A role for IgG anti-IgE as an activator of mast cells and basophils was also proposed in atopic dermatitis [26]. Other non-immunoglobulin histamine-releasing factors were also proposed, notably an IgE-dependent histamine-releasing factor [27] and a cytokine-like factor [28].

Evidence that serum histamine-releasing activity in chronic urticaria is due to an autoantibody

The ability of sera from some but not all patients with chronic idiopathic urticaria to cause a weal and flare reaction upon an autologous intradermal injection was first reported by Grattan et al. in 1986 [29]. They showed a positive response in seven of 12 patients, and noted that in these patients a positive result could only be obtained if the urticaria was currently active. An example is shown in Fig. 2. Initial investigation of this activity suggested it was a histamine-releasing autoantibody with the characteristics of anti-IgE based on absorption of this activity by monoclonal IgE and inhibition by lactic acid stripping of IgE from normal human basophils [30]. It was supposed that, in patients with positive sera, the development of urticarial weals was due to the ability of these antibodies

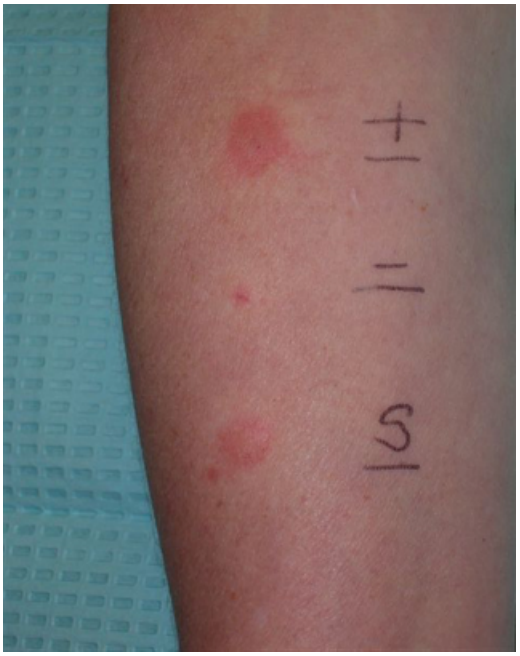

Fig. 2. Autologous skin test depicting a positive control weal at the top, a negative saline control at the centre, and a positive reaction with serum of a patient with chronic urticaria.

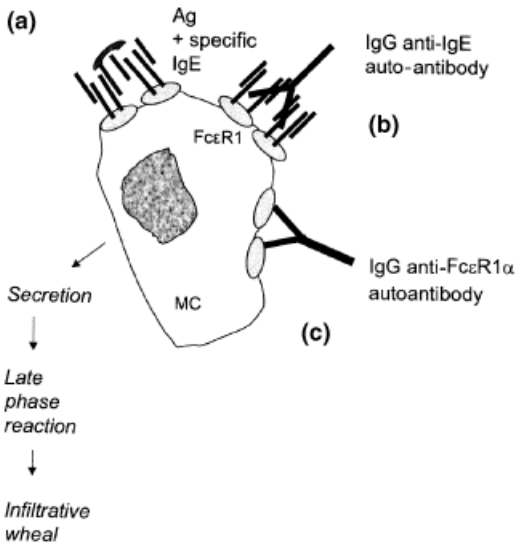

Fig. 3. A diagrammatic representation of mast cell activation by (a) an antigen cross linking IgE; (b) IgG anti-IgE antibody as seen in 5–10% of patients with chronic urticaria; and (c) IgG anti-IgE receptor antibody directed to the α subunit as seen in 40% of patients with chronic urticaria.

to cross link dermal mast cell-bound IgE, causing mast cell activation and histamine release (see Fig. 3b).

Further analysis of histamine-releasing activity of sera from four patients with chronic urticaria revealed that it consisted of IgG, or less commonly IgM, with novel epitope specificities. Inhibition experiments, using the human recombinant extracellular fragment of the

high-affinity IgE receptor (FcεRI) α subunit (FcRIα), identified IgG autoantibodies directed against FcεRI. It was proposed that these autoantibodies cross linked adjacent α subunits of FcεRI or dermal mast cells and basophils [3] (Fig. 3c), leading to activation, a potentially important initiating mechanism for chronic urticaria. We subsequently studied 165 patients with chronic idiopathic urticaria, 105 of whom had a positive autologous serum skin test. Of these sera, 43 (26% of all urticaria patients studied) released histamine from high and low IgE donor basophils, indicating the presence of functional anti-FcεRIα autoantibodies, anti-IgE autoantibodies or both [4]. Eight patients' sera reacted only with basophils from a high IgE donor suggesting that these patients possessed autoantibodies reacting with IgE. Sera from 19 healthy donors were non-reactive against basophils of low or high IgE donors. In a subsequent study, autologous serum skin test-positive sera from 12 patients with chronic urticaria caused IgG-mediated histamine release from dermal mast cells of healthy donors that could also be inhibited by human recombinant FcεRIα [4]. These data, taken together with the histological finding of dermal mast cell degranulation following an intradermal injection of autologous serum [31], represent compelling evidence that anti-FcεRIα autoantibodies are relevant to the pathogenesis of chronic idiopathic urticaria. Recently, Sabroe et al. [32] have classified sera from 75 patients with CIU into five subsets: immunoreactive histamine-releasing anti-FcεRI autoantibodies (26%); immunoreactive non-histamine-releasing anti-FcεRI autoantibodies (15%); anti-IgE autoantibodies (9%); sera containing a non-immunoglobulin mast cell-specific histamine-releasing factor [4] (9%), and sera with no identifiable factor (41%). Positive autologous serum skin tests were strongly associated with histamine-releasing anti-FcεRI autoantibodies, and no autoantibodies were detected in healthy subjects or in patients with physical urticarias [32].

Fiebiger et al. [5] used human recombinant FcεRIα and Western blotting to demonstrate that 37% of sera of 32 patients with chronic idiopathic urticaria contained immunoreactive anti-FcεRIα autoantibodies and in most cases these antibodies showed functional histamine-releasing activity. No immunoreactivity was found in sera of healthy subjects or patients with atopic eczema. In a subsequent publication [33], the same laboratory showed that anti-FcεRIα immunoreactivity could be detected in the serum of patients with other autoimmune disease including pemphigus vulgaris, bullous pemphigoid, dermatomyositis, and systemic lupus erythematosus. However, unlike the anti-FcεRI autoantibodies found in chronic urticaria, which are mainly of the IgG1 or IgG3 subtypes, anti-FcεRI autoantibodies in these other autoimmune disorders were non-functional (non-histamine releasing) and predominantly of the IgG2 or IgG4 subtypes. Similar results were reported by Kaplan's groups in 1996 [6]. In 50 patients with chronic idiopathic urticaria, these authors used a rat basophil leukaemia cell line expressing FcεRIα to demonstrate the presence of functional (β-hexosaminidase-releasing) anti-FcεRI autoantibodies in sera of 38 (76%). All but one of the 20 healthy control subjects was negative in this assay. However, when human basophils were used as indicator cells, sera from 20 to 50 patients (40%) with chronic urticaria but only one of 19 healthy controls released histamine. Later studies found immunoblotting to be a less reliable method for identification of patients with functional IgG anti-IgE receptor antibody with a significant false positive consisting of antibody (primarily IgG2) that bound a cloned α subunit by immunoblot, but did not cause histamine release [7]. This study cast doubt on the IgG subclass analysis reported by Fiebiger et al. [3], and the authors proceeded to purify the IgG subclasses from patients' IgG containing the functional IgE receptor antibody. The results confirmed IgG1 and IgG3 as the major subclasses containing the functional antibody [34]. Many patients have IgG2 anti-FcεRIα but none of these released histamine from donor basophils. This may relate to the group of subjects described by Sabroe et al. [32] in whom immune reactive antibody seemed to be present, but was not functional.

Horn et al. [35] detected anti-FcεRIα antibodies in sera from healthy donors using a recombinant protein consisting of two moieties of the extracellular part of human FcεRIα, flanking one moiety of human serum albumin. Although the affinities of these autoantibodies against recombinant FcεRIα were low, healthy donor sera containing these antibodies showed histamine-releasing activity. However, these autoantibodies were cross reactive with the tetanus toxoid, and demonstration of histamine-releasing activity was dependent on pre-treatment of donor basophils with IL-3 and stripping the cells of bound IgE. The significance of these autoantibodies, whose existence has yet to be independently confirmed, requires further examination. Attempts to eliminate antibody to the IgE receptor by incubation with the tetanus toxoid by Kaplan's groups (unpublished observations) failed while absorption with the cloned α subunit reduced or eliminated the activity.

Mode of action of anti-FcεR1 autoantibodies

Kaplan has also addressed the issue of complement involvement in autoantibody-mediated histamine release in autoimmune urticaria [7, 36]. Earlier work [3, 4] suggested that release of histamine from mast cells and basophils by anti-FcεRI autoantibodies was due to direct cross linking of adjacent α-chains of FcεRI on the surface of these cells, without complement involvement. That complement activation may be involved was suggested by the earlier identification of IgG1 or IgG3 as the principal

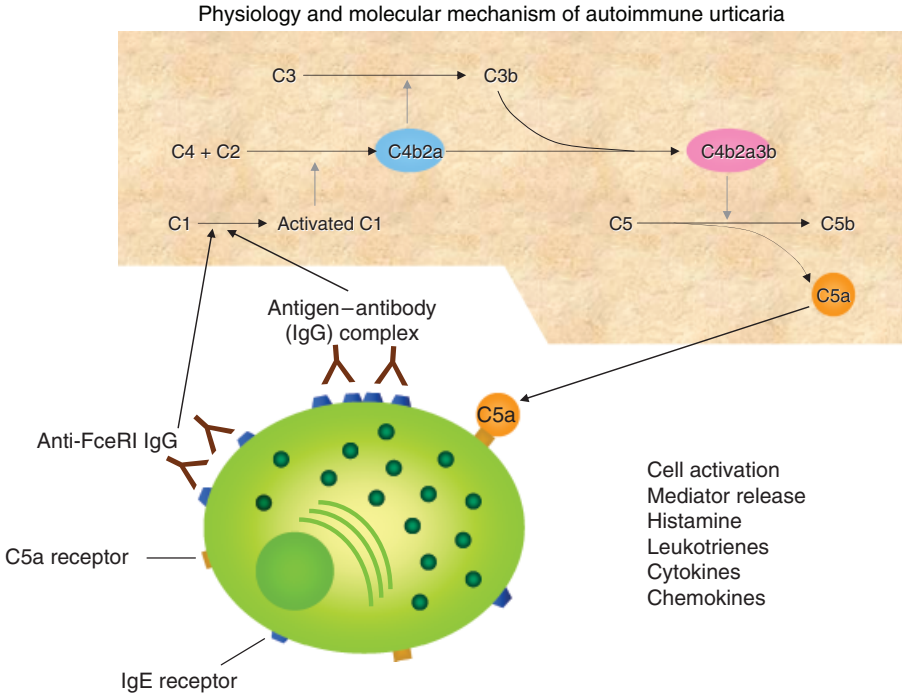

Fig. 4. A diagrammatic representation of mast cell activation by the IgG anti-IgE receptor antibody. If two Fc regions of the IgG are in close enough proximity, the first component of complement is activated, because this forms an immune complex. Activation of C4, C2, C3, and C5 ensues with the release of C5a and resultant augmentation of histamine release upon binding to the C5a receptor.

immunoglobulin subtypes in autoimmune urticaria [33]. Further evidence supporting a role for complement activation derives from histamine release experiments using highly purified IgG anti-FcεRI, and decomplemented sera deficient in either C2 or C5. It was found that whole sera from patients with chronic urticaria but not complement-deficient sera, released histamine from dermal mast cells. It was further found that C5a may play a key role because *in vitro* release of histamine from normal human basophils was dependent on the concentration of C5a and was inhibited by an antibody to the C5a receptor [37]. It was concluded that the release of histamine from dermal mast cells or basophils by anti-FcεRI autoantibodies was augmented primarily by C5a activation. Such studies emphasize the geometric requirement at the cell surface for activation (Fig. 4). Two α subunits must be bridged by the IgG antibody to activate the cell; however, two IgG molecules in tandem are required for activation of the first component of complement. Thus, four α subunits in proximity are bound by antibody to lead to C5a formation. Conversely, saturation of all α subunits by incubation with the E myeloma protein renders the IgG anti-receptor antibody ineffective [2]. Thus, the percent occupancy of the α subunit by IgE is a determinant of cell activation although a small percentage of the anti-receptor antibody may bind to an epitope that is still available in the presence of IgE [1]. This involvement of C5a could also explain the otherwise puzzling lack of clinical evidence of pulmonary involvement in autoimmune urticaria, because lung mast cells but not dermal mast cells are deficient in C5a receptors [38]. However, bronchial hyperresponsiveness to methacholine challenge has been observed [39] regardless of whether respiratory allergy is present. The mechanism by which this relates to the pathogenesis of chronic urticaria is not clear.

Additional observation regarding autoimmunity and/or inflammation in chronic urticaria

Pucetti et al. [40] have reported activation of eosinophils by stimulation with antipeptide antibodies that are contained within the CD23 antigen present on FcεRII. Evidence was provided that eosinophil degranulation can cause secondary degranulation of basophils as a result of the release of eosinophil major basic protein. These data have not been confirmed but are of considerable interest. The serum-derived eosinophil-activating factor was found in over 70% of patients with chronic urticaria based on the ELISA methodology but insufficient sera of patients were tested for basophil histamine release to draw any conclusions. Because serum-derived basophil histamine release attributable to anti-FcεRI antibodies does not exceed 45% and functional anti-FcεRI was not assayed, it is difficult to know the degree to which this antibody might be pathogenic.

Asero and colleagues have published a series of articles demonstrating activation of the extrinsic coagulation

cascade in patients with chronic urticaria [41, 42]. They have shown that plasma levels of Factor VIIa (but not Factor XIIa), prothrombin fragment 1+2, (indicating conversion of prothrombin to thrombin) and D-dimer (indicating fibrinolytic degradation of fibrin) are elevated in patients with chronic urticaria presumably due to release of tissue factor. Urticarial skin did demonstrate immunoreactivity for tissue factor while normal skin did not and the levels of D-dimer and prothrombin fragment 1+2 were more prominently elevated in patients whose chronic urticaria was particularly severe [43]. Our interpretation is that endothelial cell activation leads to release of tissue factor with activation of the extrinsic coagulation cascade with secondary fibrinolysis. These data are similar to the observations reported previously in patients with systemic vasculitis, and patients with scleroderma in particular.

The authors also refer to observations that an intradermal injection of citrated plasma (rather than serum) in patients with chronic urticaria leads to a significant increase in vascular permeability [40]. Interpretation of these latter data is difficult, not the least of which is absence of evidence for thrombin-dependent activation of basophils or mast cells in humans, and patients with chronic urticaria in particular. Virtually all the data use rodent models using thrombin concentrations that do not relate to levels in human plasma [44, 45]. Furthermore, thrombin is inactivated extremely rapidly by plasma inhibitors and may not reach levels sufficient to interact with basophils or cutaneous mast cells despite measurable amounts of prothrombin conversion to thrombin. Lastly, the skin test using plasma rather than serum was reported to be positive in 86% of patients and yet there has been no attempt to characterize the plasma factor. As this skin test is performed, any thrombin present should be complexed to inhibitors and inactivated.

Cellular infiltrate

Mast cell degranulation initiates the inflammatory process in autoimmune chronic urticaria and is also assumed to do so in idiopathic chronic urticaria. Evidence for increased numbers of mast cells in chronic urticaria has been presented [46, 47], but there are also publications indicating no significant differences from normal [48]; these studies did not discriminate the autoimmune from the idiopathic groups. However, no alternative mechanisms for mast cell degranulation in the idiopathic groups have been suggested to date. Yet the histology of the lesions in the two groups differs in only minor ways. 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 [46, 49]. Granulocytes are quite variable but are plentiful if the lesion is subjected to a biopsy early in its development. Both neutrophils and eosinophils are present [50, 51], although the degree of eosinophil accumulation varies considerably [49]. The study by Sabroe et al. [51] demonstrated that activated eosinophils were found more frequently and were more persistent in patients without autoantibodies rather than with autoantibodies in older (>12 h duration) weals. Even when eosinophils are not evident, major basic protein can be identified within lesions (in at least two-thirds of the patients), which most likely represents evidence of prior eosinophil degranulation [52]. The presence of basophils has also been demonstrated by using an antibody (BB1) that is specific for this cell type [53]. Thus, the infiltrate resembles that of an allergic late-phase reaction. Endothelial cell activation is suggested by the presence of intercellular adhesion molecule 1 and E-selectin in biopsy specimens of urticarial lesions [54]. Sources of chemokine include the 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-β but also by the vasoactive factors – for example, histamine, and leukotrienes released from activated mast cells [55]. Not only does complement activation and the release of C5a result in augmented mast cell (and basophil) histamine release, but C5a 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 levels [56] in patients with chronic urticaria provides indirect evidence of lymphocyte activation, basophil activation or both.

A direct comparison between cutaneous late-phase reactions and chronic urticaria revealed that infiltrating cells had characteristics of both T-helper type 1 (Th1) and Th2 cells, with the production of IFN-γ by the former cells and IL-4 and IL-5 by the latter [52]. Alternatively, this might represent activated Th0 cells (i.e. activated $CH4^+$ lymphocytes that have not differentiated into Th1 or Th2 cells). When the histology of lesions of autoimmune and idiopathic chronic urticaria was compared [51], the autoimmune subgroup had greater prominence of granulocytes within the infiltrate, whereas other infiltrating cells were quite similar in the two groups; a small increment in cytokine levels was seen in the autoimmune group, and greater tryptase positivity (indicative of less degranulation) was observed in the autoantibody-negative group. The patients with autoimmune chronic urticaria generally had more severe symptoms than those with idiopathic chronic urticaria [32].

Chronic urticaria as an autoimmune disease

At least 30–50% of patients with chronic idiopathic urticaria have detectable functional anti-FcεRI or anti-IgE

autoantibodies and these patients show, as already mentioned [16], an increased frequency of HLA DR alleles characteristically associated with autoimmune disease. In the subset that possesses these autoantibodies, the evidence that they are pathogenic is persuasive and can be summarized as follows: functional (histamine-releasing) anti-FcεRI autoantibodies are not found in healthy people, allergic subjects or in patients with other types of chronic urticaria [3, 4, 6, 57], the antibodies release histamine from mast cells and basophils [3–7] and cause wealing upon intradermal injection in a healthy volunteer [3]; the plasma levels of the autoantibodies correlate well with disease activity [58, 59]; and removal of the autoantibody leads to remission. The antibody can be partially purified and shown to be present in IgG1 and IgG3 enriched fractions [34]. An additional autoimmune phenomenon is also seen in this subgroup including antithyroid antibodies and a high incidence of positive ANAs with a speckled pattern (A. P. Kaplan, unpublished observation). None had systemic lupus erythematosus. Standard criteria for definition of an autoimmune disease require that, in addition to the above, reproduction of the disease in experimental animals be performed [60], and this has not yet been done using anti-FcεRI autoantibodies; therefore, strictly the evidence should be regarded as convincing, but short of fully proven. That autoantibodies against receptors can cause disease is by no means a novel concept, recognized examples including myasthenia gravis (acetylcholine receptor) and insulin-resistant diabetes mellitus (insulin receptor). In these and other similar examples, receptor activation is blocked or downgraded. Receptor activation due to a receptor-specific autoantibody is less common and autoimmune urticaria now joins Graves' disease (autoantibody against the thyroid-stimulating hormone receptor) as an example of this less common receptor-mediated cell activation autoimmune phenomenon. These interesting issues have been discussed previously in greater detail [59, 60]. It should also be noted that virtually every autoimmune disease has some subjects with positive antibodies and not disease, which may explain the occasional positive basophil histamine release reported in subjects without urticaria [61]. Nevertheless, Kaplan and Joseph [57] recently published a typical assay in which no positives were found in 35 allergic subjects who did not have urticaria, and 54 positives were found out of 104 chronic urticaria patients tested (Fig. 5). The small amount of histamine seen in the 'idiopathic' group may represent a weak histamine-releasing factor present or, more likely, represents the serum histamine level of patients, which was not subtracted. It is not present in controls. The same autoantibodies have been found in children with chronic urticaria with a 47% incidence (37 positives in 78 children) and none in 33 children with atopic dermatitis, used as a control [62].

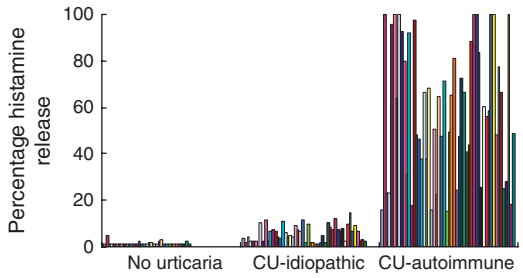

Fig. 5. Performance of the basophil histamine release assay to diagnose chronic autoimmune urticaria in the laboratory of one of us (A. K.). No significant histamine release is seen in 30 normal controls. Over one hundred chronic urticaria patients sorted into those who are clearly positive (>20% histamine release) in the right, and those with low histamine release (generally 15% or less) who are negative and remain in the idiopathic group. A low equivocal value at 16–18% were placed in the negative group.

Concluding comments: additional considerations

Patients with chronic urticaria are currently divided into those with autoimmune manifestations (anti-IgE receptor, 35–40%; anti-IgE, 5–10%) with or without antithyroid antibodies (antithyroglobulin, anti-peroxidase), termed chronic autoimmune urticaria. Although these antibodies are considered to be pathogenic, i.e. responsible for cutaneous mast cell activation as an initiating stimulus for chronic urticaria, it is clear that chronic urticaria is present in 50–60% of patients in the absence of such antibodies. Such patients remain idiopathic (chronic idiopathic urticaria) where the initiating stimulus is not known. The abnormal basophil responsiveness described in sub-populations of patients with chronic urticaria does not provide an initiating mechanism for hive formation, but may represent an associated abnormality that is a consequence of having urticaria. Although patients with chronic autoimmune urticaria are somewhat more severe than those considered to be idiopathic [32] with a more substantial inflammatory cell infiltrate but fewer (EG2+) eosinophils observed histologically [51] the differences are quantitative. Qualitatively, the two sub-populations are essentially similar.

Historically, considerations regarding the aetiology/pathogenesis of chronic urticaria included a psychophysiologic reaction associated with anxiety, food allergies, reactions to food additives, pseudoallergy, or a manifestation of an occult infection.

The issue regarding food allergy has been discussed recently in some detail [63]. Food allergy is a recognized cause of acute urticaria, but the role of food components in chronic urticaria is controversial. In a recent textbook on urticaria [64], Henz describes food protein preservatives and colouring agents as major causative factors in chronic urticaria. The concept of food additives as a cause of chronic urticaria first become popularized in the

European literature of the 1970s and 1980s by Juhlin and Michaelsson and later by Doeglas and by Supramanian and Warner [65–67]. These studies involved challenge testing but were not adequately placebo-controlled, and the reproducibility of apparently positive reactions was not investigated although positively reacting patients were said to respond subsequently to dietary restrictions. The experience of one of us (M.W.G.) in the routine use of a placebo-controlled single-blind challenge testing for food additive intolerance, over a period of 20 years, indicates that patients who can *reproducibly* be shown to react to a food additive are extremely rare and we agree with Mathews [68], who stated in 1983 that 'as a cause of chronic urticaria or angioedema food allergy can only be rarely implicated'. Pseudoallergy is defined as the foodstuffs containing chemicals thought to be responsible for sustaining chronic urticaria [69]. There is no associated IgE-dependent hypersensitivity and no molecular mechanism has been discerned.

Pseudoallergens include artificial food dyes, preservatives, and sweeteners [70], aromatic compounds in wine, tomatoes, and spices [71] as well as phenols such as *p*-hydroxybenzoic acid, citrus and orange oil, salicylates, etc. The remission rate attributed to elimination diets varies from 30% to 90%, and yet a double-blind placebo-controlled food challenge with these substances contained in capsules failed to reproduce urticaria [72, 73]. Possibly certain of these pseudoallergens may exacerbate pre-existing urticaria, but evidence of a primary aetiological role is unconvincing. The authors have no personal experience with this approach.

Thyroid function in chronic idiopathic urticaria

Hashimoto's thyroiditis and less commonly Graves' disease show a positive association with chronic idiopathic urticaria. Antithyroid autoantibodies are found in 27% of patients with chronic urticaria and 19% have abnormal thyroid function. However, there is no convincing evidence that treating the underlying thyroid dysfunction alters the course of the accompanying urticaria. Thyroid disease and chronic urticaria are frequently associated but there is no evidence that the thyroid autoantibodies are pathogenic in the context of chronic urticaria. The significance of the association lies in the separate autoimmune mechanisms found in both disorders.

Other claimed causative factors in chronic idiopathic urticaria: *Helicobacter pylori*

The numerous anecdotal reports of different 'causes' of chronic urticaria that continue to appear in the literature bear witness to the frustrations of clinicians dealing with the disorder. It is pointless to itemize these, but one microorganism, *H. pylori*, is worth a brief mention because of its possible significance, not as a direct cause of chronic urticaria, but because of its possible relevance to autoimmunity. This topic has recently been reviewed [74]. Evidence of *H. pylori* infection is found in up to 50% of the general population in most regions of the world and in at least 30% of patients with chronic idiopathic urticaria. However, treating the *H. pylori* has no significant effect on the course of the chronic urticaria [75]. Recent evidence has demonstrated that *H. pylori* infection induces autoantibody formation due to the immunogenicity of its cell envelope polysaccharide Lewis x and y blood group antigens. Autoantibodies are formed by molecular mimicry analogous with the role of *Campylobacter jejuni* in the Guillain–Barre syndrome. *H. pylori* also induces HLA-DR expression on gastric epithelium, enabling these cells to behave as antigen-presenting cells. The interesting possibility therefore arises that *H. pylori* might have an indirect role in the aetiology of chronic idiopathic urticaria by reduction of immune tolerance, which might lead to induction of autoantibody formation including anti-FcεRIα autoantibodies.

Finally, approaches to the diagnosis and treatment of chronic urticaria have been recently reviewed [76, 77] and guidelines have been published [78]. Identification of the autoimmune sub-population is best carried out by histamine release from donor basophils but this is primarily a research tool. Some laboratories have begun to offer this test; quantitation of an activation-dependent surface marker on basophils is an alternative [79]. The autologous skin test can be performed in a private office environment and identifies about 30–35% of subjects with a circulatory histamine-releasing factor (usually antibody, but perhaps not exclusively so). Studies of patients' basophil responsiveness remain a research tool.

Therapy is dependent on the use of non-sedating antihistaminics; first-generation antihistamines can be attempted should a double dose of the above fail. Sedation becomes problematic, but may be safer for most (with appropriate counseling) than the side effects of other agents. Low dose corticosteroid (no more than 10 mg/day with a taper by 1 mg/week) can be safely used for severe persistent symptoms while cyclosporine is the best-studied (and effective) non-steroidal agent for poorly responsive chronic urticaria [80]. Omalizumab (anti-IgE) has been used effectively in the autoimmune subgroup [81] as reported in a single-blind placebo-controlled study of 12 patients; additional uncontrolled observations also suggest efficacy [82, 83]. Theoretically, binding plasma IgE leads to down-regulation of the IgE receptor (the antigen in this instance), such that basophil or cutaneous mast cell responsiveness to the anti-receptor antibody is diminished or eliminated [84]. Finally, many other agents have support in the literature, e.g. hydroxychloroquin, dapsone, colchicine, methotrexate, and sulphasalazine. None of these approaches have been studied with

appropriate double-blind placebo control groups and they are unreliable at best, and possibly no more effective than placebo. However, many of these are particularly useful for urticarial vasculitis.

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