

Urticaria and Autoimmunity: Where Are We Now?

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Abstract There is considerable debate whether chronic urticaria is an autoimmune disease or whether its features suggestive of autoimmunity are epiphenomena. A plethora of circumstantial evidence suggests that chronic urticaria is an autoimmune disease, but criteria to establish autoimmunity require direct proof and indirect evidence, and these are lacking in chronic urticaria. Current approaches to assessing for autoimmunity in vivo via the autologous serum skin test, and in vitro via either basophil histamine release or the basophil activation test are widely utilized, but the results of these tests have limited impact on prediction of the clinical course and efficacy of treatments. Recent guidelines for diagnosing autoimmune urticaria have been proposed, but further investigation is needed.

Keywords Urticaria · Hives · Autoimmunity · Autologous serum skin test · Basophil histamine release · Thyroiditis · Witebsky's postulates

Introduction

Chronic urticaria (CU) is defined as spontaneous urticaria for 6 weeks or greater without a known allergic precipitant. In 35–40 % of cases, an autoimmune phenomenon is thought to be responsible [1]. Despite evidence that chronic urticaria is both autoimmune in nature and can coexist with other autoimmune diseases, there is limited evidence that this is relevant to either prognosis or treatment. This review will outline the current evidence that chronic urticaria is an autoimmune disease, based on Witebsky's postulates for the definition of an autoimmune disease. It will also address the data concerning

in vitro and in vivo testing for autoimmunity and the application of these data to treatment and prognosis of patients suffering from the disease.

Criteria to Establish Autoimmunity

Witebsky's Postulates

Witebsky's postulates are a set of criteria that help to determine whether a disease is autoimmune in etiology. Witebsky proposed his original postulates in 1957, modeled on Koch's postulates, and Rose and Bona revisited them in 1993 [2]. Witebsky's postulates require that three criteria be satisfied to prove that a disease is autoimmune in nature: direct proof, indirect evidence, and circumstantial evidence.

Direct Proof

Direct proof involves the transfer of an autoantibody from an affected individual to a healthy individual, which results in development of disease in the healthy individual. Given the risk involved from the transfer of pathogenic autoantibodies to a healthy individual, few examples of direct proof exist, even in diseases widely accepted to be autoimmune in nature. In selected autoimmune diseases, including Graves disease and myasthenia gravis, direct proof comes from transfer of antibodies via the placenta from a mother with autoimmune disease to her healthy infant [2]. There are no reported examples of transplacental transfer of chronic urticaria. While there is no direct proof of transfer of chronic urticaria, there has been a case report of passive transfer of a positive autologous serum skin test (ASST). A patient without chronic urticaria had no reaction to autologous serum, but developed a characteristic wheal and flare with serum from a patient with chronic urticaria [3]. A case report of transfer of ASST reactivity from a child with chronic urticaria to her unaffected mother was limited by a lack of a control with the mother's own serum [4]. Attempts to

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identify pathogenic autoantibodies responsible for a positive ASST in chronic urticaria will be discussed later.

Indirect Evidence

Indirect evidence requires the reproduction of the autoimmune disease in an experimental animal model. There is no animal model for chronic urticaria, and chronic urticaria cannot satisfy this criteria. With little direct proof and a lack of indirect evidence, the rationale for chronic urticaria as an autoimmune disease relies almost completely on circumstantial evidence.

Circumstantial Evidence

Circumstantial evidence for autoimmune disease is based on clinical clues, including an association with other autoimmune diseases within the same individual or family, lymphocytic infiltration of the target organ, association with a particular MHC haplotype, and response to immunosuppression [2]. Chronic urticaria fulfills essentially all of the circumstantial evidence criteria. It is associated with other autoimmune diseases, particularly thyroiditis [5•]. It involves T lymphocytic infiltration in lesions and ASST wheals [6]. Specific MHC haplotypes have been associated with chronic urticaria, with the best evidence for HLA DRB1*04 [7]. Finally, it often responds to immunosuppression, with the greatest body of evidence for cyclosporine, which acts by inhibition of T cell activation, and can cause lasting remission of disease [8, 9, 10•].

Association with Other Autoimmune Diseases

The association between chronic urticaria and other autoimmune diseases was examined in a recent large retrospective database review, which found that an autoimmune diagnosis is common within 10 years of a CU diagnosis [11••]. In this study, that spanned 17 years and included over 20,000 patients, a diagnosis of CU was associated with an increased odds ratio for hypothyroidism (17.3), hyperthyroidism (28.8), and the presence of thyroid autoantibodies. Women with CU also had increased odds ratios of rheumatoid arthritis, Sjogren's disease, celiac disease, type 1 diabetes mellitus, and systemic lupus erythematosus. Autoimmune diseases were mostly diagnosed in the 10 years after CU diagnosis, and not in the 6 months after CU diagnosis, which suggests they were not discovered during the initial workup of CU. The authors noted that correlation may be due to a shared susceptibility to autoimmune diseases and that autoantibodies often precede the onset of autoimmune diseases by many years [11••]. While this was the largest study of the association of autoimmunity and CU, many smaller studies

and case reports confirm these findings in specific autoimmune diseases.

Thyroiditis is the autoimmune disease with the strongest link to CU. A meta-analysis of studies that examined the link between thyroid autoimmunity and CU found the prevalence of at least one positive antithyroid antibody in CU was 20 %, compared with 5.5 % of control subjects [5•]. In autoimmune diseases associated with thyroiditis, such as systemic lupus erythematosus, up to 30 % of patients have thyroid autoantibodies [12]. It is uncertain whether the association of CU and thyroid autoantibodies is a marker of general susceptibility to autoantibody formation and autoimmunity, as with lupus, or whether thyroid disease has an effect on chronic urticaria.

The underlying mechanism of concomitant thyroid disease and urticaria is not well established. There is no evidence of epitopic cross-reactivity between antithyroid antibodies and other autoantibodies found in CU, and antithyroid antibodies alone are unable to influence a mast cell line's activation [13]. Autoantibodies against the complement controller domain of TPO can activate complement via the classical pathway, and elevated serum C4a levels at baseline normalized in remission after treatment with levothyroxine [14]. This suggests a potential direct role for antithyroperoxidase antibodies in the pathogenesis of CU, and challenges the concept that chronic urticaria may be an autoimmune disease due to antibodies that activate mast cells and basophils via FcεRIα.

Remission of chronic urticaria symptoms after treatment with levothyroxine in patients with concomitant thyroid autoimmunity has been reported, even in euthyroid patients. Symptoms recurred with discontinuation of levothyroxine, and patients without thyroid autoimmunity did not improve [15]. Most allergists are aware of the connection between thyroid autoimmunity and CU, and they check antibody levels in most of their patients, but they do not start most patients on levothyroxine [16]. A placebo-controlled trial of levothyroxine to treat CU in euthyroid patients found that, after 12 weeks, there was no significant difference in symptom improvement with antihistamines plus levothyroxine in a dose that suppressed TSH to <0.5 μIU/mL, compared to treatment with antihistamines alone [17]. While this study included only 15 subjects, a larger retrospective review noted no difference in improvement in urticarial activity score after 6 months in CU patients with hypothyroidism treated with levothyroxine to achieve a euthyroid state versus those without hypothyroidism who had usual treatment [18].

Besides thyroiditis, autoimmune diseases linked to CU include rheumatoid arthritis, Sjogren's disease, celiac disease, type 1 diabetes mellitus, systemic lupus erythematosus, vitiligo, pernicious anemia, juvenile rheumatoid arthritis, and Raynaud's phenomenon [19••]. It is possible not only to find concomitant autoimmune diseases in patients with CU but to also find serologic markers associated with CU in

patients with other autoimmune diseases. When the Chronic Urticaria (CU) Index (IBT Laboratories, Lenexa, KS, USA), a test of basophil histamine release using sera from patients, that is elevated in some CU patients, was checked in patients with other autoimmune diseases, 23 % of patients with systemic lupus erythematosus had an elevated level, compared with 33 % of CU patients, 15 % of controls, and 3.7 % of rheumatoid arthritis patients [20]. This suggests that patients with systemic lupus erythematosus may have autoantibodies that function similarly to those found in CU in vitro, but have different effects in vivo.

Lymphocytic Infiltration of the Skin

Chronic urticaria involves T lymphocytic infiltration of the skin, both in urticarial lesions and in autologous serum skin test wheals. In patients with chronic urticaria, biopsies of autologous serum skin test wheals demonstrate significant T cell infiltration 24 h after the test. T cells are predominantly CD4⁺ at 24 h, but decline by 48 h [6]. In comparison to the skin of nonatopic controls, biopsy of urticarial lesional skin demonstrates greater numbers of intradermal and epidermal CD3⁺ cells, including CD4⁺, CD8⁺, and CD25⁺ cells. The cytokine profile of the T cells is a TH₀ profile, with increased IL-4, IL-5, and IFN- γ compared to controls. Lesions in patients with CU had a similar cellular infiltrate as that in found in allergen-induced late-phase reactions [21].

Major Histocompatibility Complex and other Genetic Associations

The major histocompatibility complex (MHC) is crucial for antigen presentation to and recognition of self by T cells. As in autoimmune diseases such as rheumatoid arthritis and SLE, chronic urticaria has been associated with specific MHC class I and II types. HLA-DRB1*04 (DR4), and its associated allele HLA-DQB1*0302 (DR8), was found in a significantly higher percentage of CU patients than controls in Britain, and this finding was confirmed in a Turkish population [7, 22]. In another study of Turkish patients, HLA-DQ1 and HLA-Bw4 were found to be associated with CU [23]. HLA-B44, HLA-DRB1*01 and HLA-DRB*15 have also been associated with CU [24]. In a study of Brazilian patients, HLA-B*50 was found to be more prevalent in CU than in the healthy population of the region [25]. The heterogeneity in the reported associations, although this may be accounted for by ethnic and regional variation, limits the interpretation of these data.

Other genetic associations have been described outside of MHC associations. Polymorphisms in *PTPN22* gene, which encodes the protein tyrosine phosphatase-22 that affects the responsiveness of T and B cells, have been implicated in many autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, and autoimmune thyroid

disease [26]. Variant SNPs in *PTPN22* have been found at a higher prevalence in CU than in healthy controls and may predispose to CU, although the SNPs are differently located from those implicated in other autoimmune diseases [27].

Response to Immunosuppression

Like many autoimmune diseases, chronic urticaria responds to immunosuppression. The greatest body of evidence is for cyclosporine, which works by inhibition of T cell activation and is the only immunosuppressant that has been evaluated in double-blind, randomized, placebo-controlled studies in CU [9, 28]. In a review of studies utilizing cyclosporine, response rates ranged from 40 to 100 % [10•]. Cyclosporine has also been shown to cause lasting disease improvement or remission 10 years after an initial course, with 60 % of patients experiencing sustained symptom resolution or improvement [29]. Mycophenolate mofetil, which works by inhibiting T and B cell proliferation, has also shown efficacy in the treatment of CU [30, 31]. There are selected reports of other immunomodulatory medications' utility in CU, including sulfasalazine, hydroxychloroquine, dapsone, and methotrexate, although the published evidence is limited [32, 33]. Corticosteroids have broadly immunosuppressive effects and, in practice, are widely utilized as second line treatment when symptoms are refractory to antihistamines, although published data are limited [34].

Both direct removal of pathogenic antibody through plasmapheresis and treatment with IVIG have been successful in accepted autoimmune diseases, and in small studies in CU. Plasmapheresis caused improvement of symptoms in 6 of 8 patients after one treatment [35]. IVIG (dosed at 0.4 mg/kg for 5 days) in ten patients caused remission in 50 % and improvement in all but one subject. Two had sustained remission for at least 3 years, and all had ≥ 6 weeks of remission [36]. Targeted B cell therapy with rituximab, a chimeric murine/human monoclonal antibody that targets CD20 on B cells and has been used successfully in autoimmune diseases, allowed for months of disease remission in case reports of a child and an adult with CU [37, 38].

Testing for Autoimmune Urticaria

Chronic urticaria does not fit all of the criteria in Witebsky's postulates, with limited direct proof, no indirect evidence, but significant circumstantial evidence (Table 1). However, the underlying pathology in autoimmune disease is a self-reactive lymphocyte clone, and Witebsky's postulates define criteria that result from activity of this clone. One way to demonstrate the presence of such a clone is isolation of pathogenic autoantibodies, and much of the "autoimmune" testing for chronic urticaria has focused on identification of

Table 1 Evidence for chronic urticaria as an autoimmune disease

Witebsky's postulate	Evidence in chronic urticaria	Chronic urticaria fulfills Witebsky's postulate
1. Direct proof	No (except for 2 case reports)	No
2. Indirect evidence	No	No
3. Circumstantial evidence:		
a. Association with other autoimmune diseases	Thyroiditis and others	Yes
b. Lymphocytic infiltration	T cells in dermis	Yes
c. MHC association	HLADR4 and others	Yes
d. Response to immunosuppression	Cyclosporine, mycophenolate, plasmapheresis/IVIG, rituximab	Yes

autoantibodies or surrogate markers of their activity. This has been accomplished by both in vivo testing with the autologous serum skin test and autologous plasma skin test; in vitro testing with basophil histamine release and markers of basophil activation, and in vitro by immunoblot or ELISA.

Autologous Serum Skin Test (ASST)

The first description of the autologous serum skin test was in 1946, where 53 of 956 (5.5 %) of inpatients tested with injections of their own serum had a positive result. Six of those patients had a history of urticaria, and the remainder had a history of asthma or another skin condition [39]. While the technique differed from that used in later studies, this study was the first to describe a factor in serum that would cause wheal and flare upon injection into the subject's own skin [3]. The autologous serum skin test was first described as a diagnostic tool in chronic urticaria 40 years later [40]. In this study, 7 of 12 (58 %) of subjects with CU and none of the controls had a positive ASST. After 1 year, ASST was repeated, with stored and fresh serum. Two-thirds of the subjects who had cleared their urticaria had positive results to the stored serum, with negative results to serum acquired during remission, whereas subjects with persistent urticaria had positive ASSTs to both sera [40]. This suggested that the mediator responsible for a positive ASST was present only during disease activity, and resolved in disease remission. The ASST also correlated with basophil histamine release and is reported to have a sensitivity of 65–71 % and specificity of 78–81 % for detecting the presence of histamine-releasing autoantibodies, defined as basophil histamine release ≥ 5 % [41]. Concerns were raised that the ASST may produce false positive results, as the clotting process produces bradykinin and complement activation. The autologous plasma skin test (APST) was suggested to be a superior test, with more specificity [42]. However, both tests have equal specificity and the ASST has greater sensitivity [43]. Current guidelines do not recommend the APST over the ASST [44].

Utility of the Autologous Serum Skin Test

Despite the findings that many patients with CU have a positive ASST, the utility of the ASST in CU has been questioned. These questions stem from the variability in test results in patients with clinically similar presentations, the finding that the ASST can be positive in healthy controls or those in whom disease has remitted, and the observation that the ASST is not helpful in predicting response to treatment or guiding selection of treatment. The recent ECAAI/GA²LEN consensus report on the ASST in urticaria reviewed the literature on the topic, and found that a limiting factor in comparing rates of positivity of ASST is that different criteria have been used to determine what is a positive ASST [44]. If the current criteria of a wheal diameter ≥ 1.5 mm than saline control is used, there is a 45.5 % rate of ASST positivity [44]. In studies that utilize healthy controls for the ASST, the test's results are generally negative; however, a few have reported high rates of ASST positivity in controls. In one study, the ASST was found to be positive in 30 % of patients with seasonal allergic rhinitis, 41 % of healthy controls, and 53 % of CU patients, resulting in no statistically significant difference in ASST positivity between the groups, and low sensitivity and specificity [45].

In the first description of ASST in CU, the results correlated with disease remission; however, ASST results in patients with concomitant thyroiditis can remain persistently positive. In remission, 87 % of patients without thyroiditis converted from a positive ASST to a negative ASST, but only 8 % of those with thyroiditis had a conversion in their ASST [46]. This suggests that ASST is not a good marker of disease activity, especially in those with thyroiditis. The ASST is also not useful in predicting the severity of disease or disease course. One year after a positive ASST, there was no difference in the duration or severity of symptoms, responsiveness to antihistamines, or need for corticosteroids or cyclosporine compared to subjects with a negative ASST [47].

The ASST result also does not correlate with response to treatment. Both ASST positive and negative patients respond

to cyclosporine at similar rates [48, 49]. While a positive ASST can turn negative after treatment with cyclosporine, a positive ASST after cyclosporine does not correlate with disease persistence [48]. The result of the ASST does not correlate with response to omalizumab, a monoclonal antibody against IgE. At baseline, ASST was positive in 8 patients and negative in 3 patients, and after treatment with omalizumab, despite disease remission, the ASST remained positive in 3 patients [50]. Subsequent larger studies that demonstrated the efficacy of omalizumab in CU did not report ASST results [51, 52].

While the ASST has been used historically as a marker for autoimmunity in CU, the lack of specificity of this test for patients with CU in some studies, coupled with its inability to predict response to treatment, makes the ASST a less useful test for autoimmunity in CU than was originally hoped.

Laboratory Testing for Autoantibodies

While the ASST may not be an optimal test for demonstrating autoimmunity in CU, attempts have been made to define specific autoantibodies present in CU via in vitro testing. These focused on basophil histamine release, direct isolation of antibodies, and markers of basophil activation.

Basophil Histamine Release

In 1993, Hide and colleagues evaluated sera from CU patients with a positive ASST, and found that 17 of 26 (65 %) of the sera caused histamine release from donor basophils. They demonstrated that CU sera contained IgG with histamine-releasing activity that competes with IgE for the binding region of FcεRIα, and IgE sensitization of basophils was not necessary for histamine release, as it is in most allergic diseases. The authors concluded that this was evidence for an anti-FcεRIα antibody that was able to induce activation similarly to the autoantibodies to the TSH receptor found in Graves disease [53].

Isolation of Autoantibodies

Autoantibodies to FcεRIα have been found in 35–40 % of patients with CU [1]. Antibodies to FcεRIα were found among all IgG subclasses, but only IgG1 and IgG3 were capable of causing histamine release from donor basophils

(BHR). Only IgG1 and IgG3 can fix complement, and complement inactivation by heat reduces BHR, which suggests a central role for complement [54]. Functional autoantibodies in CU are predominantly IgG3, then IgG1, with a small amount of IgG4 [55]. Antibodies to FcεRIα were found in both cutaneous (pemphigus, bullous pemphigoid) and systemic (SLE, dermatomyositis) autoimmune diseases at equal titers to CU, but they were mainly IgG2 and IgG4, and were unable to cause causing significant BHR [54].

Markers of Basophil Activation

Given the difficulty of direct isolation, other ways to identify autoantibodies have focused mainly on markers of basophil activation. Initially, CD63 was used as a marker of basophil activation, but CD203c was found to be more basophil-specific, and expression of ≥5 % had a good correlation with results of BHR and ASST. Further evidence that CD203c expression was mediated by IgG was demonstrated when depletion of serum IgG resulted in the reduction of CD203c expression from a mean of 30 % to 5 % in CU patients [56]

Utility of Laboratory Testing for Autoantibodies

The presence of autoantibodies to FcεRIα is not evidence that they are the cause of CU, and, as with the ASST, does not generally predict prognosis or response to treatment. There is one report of some correlation with severity of urticarial symptoms and laboratory testing. In this study, patients with an elevated BHR and presence of anti-FcεRIα antibody did have significantly greater symptom scores compared to those with negative tests, but the differences were very small [57].

In regards to treatment, in vitro testing has some power to discriminate between antihistamine responsive and antihistamine refractory disease, but is not predictive of utilization of immunosuppressants. The Chronic Urticaria (CU) Index (IBT Laboratories) is a commercial BHR assay, where donor basophils are incubated with sera from patients, and a value of >10 indicates significant histamine release. One group has found a correlation between a higher CU index and antihistamine refractory CU, with the median CU index 10.6 in subjects with antihistamine refractory disease, compared to 5.1 in those with symptoms controlled by antihistamines [58]. The same group found that the CU index was >10 in

Table 2 ECAAI Guidelines for diagnosis of autoimmune chronic urticaria

A positive bioassay (BHRA or basophil activation marker expression) to demonstrate functionality in vitro AND
Positive autoreactivity (by means of a positive ASST) to demonstrate relevance in vivo to MC degranulation and vasopermeability AND
A positive immunoassay for specific IgG autoantibodies against FcεRIα and/or anti-IgE (WB or ELISA) to demonstrate antibody specificity.

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80 % of patients with antihistamine and leukotriene inhibitor refractory disease versus 46 % of patients with disease controlled by those medications [59]. When using CD203c as a marker of basophil activation, there was no significant difference in use of cyclosporine or corticosteroids in the group with elevated CD203c expression, although there was a nonsignificant trend towards greater medication use and there was no information on responsiveness to treatment [60]. After successful treatment with omalizumab, 9 out of 11 patients had a decrease in their BHR, and the 1 patient who did not respond to omalizumab had an increase in BHR. However, 2 patients who responded to omalizumab also had an increase in BHR [50]. There was no laboratory testing for autoimmunity reported in the most recent studies of omalizumab [51, 52].

As with the ASST, there has been concern that the tests for basophil activation or autoantibodies in CU may be positive in patients without CU, arguing against their relevance in the disease's pathogenesis. While the median value of the CU index was higher in patients with CU (17.6) than in healthy controls (6.2), the CU index was positive in 23 % of healthy controls [61]. Another examination of CU index values found elevated levels in 15 % of healthy controls, compared with 33 % of CU patients [18]. This contrasts with earlier findings that patients without CU had nonfunctional antibodies incapable of BHR. The results of these studies could be due to the variability in and utility of the CU index itself, as there was not a correlation between the results of the CU index and identification of IgG anti-FcεRIα or IgG anti-IgE [61].

European Consensus Guidelines for Autoimmune Urticaria

The European Academy of Allergy and Clinical Immunology (ECAAI) published a position paper in 2013 evaluating the evidence for autoimmune urticaria and proposed diagnostic criteria for autoimmune urticaria [19••] (Table 2). It is not certain whether these guidelines will become standard of care, since for most practices only assays of basophil activation are available, and these tests are not well standardized.

Conclusions

Based on Witebsky's postulates, there is insufficient evidence to define chronic urticaria as an autoimmune disease. There is a significant amount of circumstantial evidence pointing to the fact that chronic urticaria is an autoimmune disease, and about half of patients have positive "autoimmune" tests in vivo and/or in vitro. Most patients with symptoms refractory to antihistamines will respond to immunosuppression; however, this response is independent of the results of their "autoimmune" testing, and the majority of

CU patients will improve on omalizumab, although it is not an immunosuppressant in the conventional sense. This might lead to the conclusion that current "autoimmune testing" is of dubious worth, as the result does not guide management of the disease. However, focused testing can reassure patients of the etiology of their urticaria, and eliminate demand for an exhaustive workup with unnecessary testing to look for exogenous causes. Broad laboratory testing in chronic urticaria has been reported to rarely yield a cause or promote a change in management [62, 63]. However, tests for autoimmune urticaria were not included in these studies, and so it is not possible to associate the low utility of other tests with tests for autoimmunity in chronic urticaria.

Despite the lack of correlation between current autoimmune testing and response to treatment, the suggestive circumstantial evidence supporting an autoimmune cause of this disease should spark new questions and theories as to the potentially undiscovered mechanisms of CU. Interest may mainly be academic at this point, but there is potential for clinical applicability in the future, particularly in light of the association of CU with autoimmune diseases later in life.

Compliance with Ethics Guidelines

Conflict of Interest Stephen C. Dreskin has served on the American Board for Allergy and Clinical Immunology; has served as a consultant for the Clinical and Safety Assessment (CISA) Network (administered by Vanderbilt University); has served as a member on the medical expert panel for vaccine review for Pfizer; has served as a member of the medical expert panel on the Division of Vaccine Injury Compensation (DVIC) for the Department of Health and Human Services; has provided expert testimony on occasional medicolegal cases; has received grant support from the National Institutes of Health, Genentech, and the American Academy of Allergy, Asthma and Immunology; has received honoraria for grant review activities from the National Institutes of Health; and has patents pending on fructose and food allergy and a diagnostic test for peanut allergy.

Jenny M. Stitt declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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