

Physiological Mechanisms of Histamine-Induced Hyposensibilization in Infectious Allergic Bronchial Asthma

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Abstract—Ascendancy therapy with histamine had a distinct clinical effect and caused stable remission in patients with infectious allergic bronchial asthma. Therapy normalized not only histamine release but also the balance of all components of the immune system. Beginning from minimum doses of histamine, gradual adaptation of the immune system was observed and normalized the immune response. To improve the clinical efficiency, it is important to control the increase of the prescribed doses of histamine. A simple test for a change in granulocyte migration to the oral cavity was proposed for this purpose. The paper discusses the probability that common mechanisms underlie immunotherapy in specific chronic allergy, ascendancy therapy with histamine in intrinsic allergy, and dosed immunotherapy in chronic inflammatory disorders.

Bronchial asthma (BA) is a typical allergic disorder and is underlain by a specific allergy or para-allergy. BA arises when an allergen evokes production of certain specific antibodies, predominantly IgE, which have affinity for mast cells and basophils and trigger the release of specific mediators, mostly histamine. In this case, the disorder is based on a specific allergy. In addition, BA arises because of activation of basophils and mast cells by different substances and effects; e.g., when calcium membrane channels are opened, this brings about a release of histamine and other mediators from the cells. In this case, the disorder is based on a para-allergy, or intrinsic allergy. Although this form (including infectious allergic asthma) accounts for about 30% of BA patients, methods of its specific pathogenetic cure are the least understood [1].

On the other hand, BA is a chronic hyperergic inflammation [2], and inflammation is known to be the main effector function of the immune system [3]. Any inflammatory process not only involves all (specific and nonspecific) immune components but also raises their activity to a higher level because the immune system, as a large system, functions as a whole. In the last decade, this has been clearly shown for BA [2].

The immune system is a complex multicomponent system, and every stage of its functioning is characterized by a certain balance of its components and their interactions, be the work of the system normal (in clinical health) or enhanced (in an inflammatory process) [3]. Any chronic disorder is underlain by a disbalance in the functioning of the whole immune system. In other words, such a disorder involves functional alterations not only of the main pathogenetic component but also of all other components of the immune system [4]. Moreover, major alterations are often observed for seemingly tangential components in some chronic processes.

This is clearly demonstrated by analysis of specific desensibilization (specific immunotherapy, SIT) in chronic allergic disorders. Although SIT is the most efficient method of curing patients with chronic allergic disorders, its clinical effect often lacks association with normalization of particular immune components (e.g., total IgE, antibodies to antigens, etc.), including those that seem to be most important for the genesis of allergy. Therefore, many specialists think that the mechanism of SIT action is still unclear.

We have proposed a principle of curing patients with various chronic inflammatory processes [4–6], assuming that, to normalize the immune response to an antigen, it is necessary first to normalize the balance of the immune system by training it via repetitive administration of an immunostimulator at threshold doses and to normalize the metabolic processes in the organism via reduction of endogenous intoxication (in contrast to normalization of a particular, altered, component of the immune system; the inadequacy of this approach has been discussed previously). In our opinion, this principle can logically account for the mechanism of SIT effects in specific chronic allergic disorders.

We have successfully applied the principle of the normalization of the immune balance for curing patients with chronic inflammatory disorders [6]. Most probably, it could also be applied to the cure of chronic allergic disorders, especially BA. The data on curing BA patients with the use of SIT support this. On the contrary, modulating a single component of the immune system (e.g., blocking certain allergy mediators or their receptors on cells) is usually effective only with continuous administration of the relevant drugs; when the administration is terminated, symptoms reappear [7]. Such curing may increase the quality of life to a satisfactory level only with constant drug administration. In contrast, long-term SIT with small increasing

doses of allergens has a prolonged post-termination effect and can lead to complete disappearance of pathological signs [2]. Such an effect is consistent only with the principle of systemic immunotherapy. This principle provides several important approaches to improvement of SIT efficiency (see below).

In Russia and other countries, administration of histamine in increasing doses (ascendancy therapy) is successfully used in intrinsic allergies (BA, urticaria). The clinical effect of this therapy is similar to that of SIT. Yet its mechanism is almost unknown [8–14]. Histamine is an extremely important mediator that is not only involved in any inflammatory reaction of the organism but is also associated with all, specific and nonspecific, components of the immune system by numerous feedbacks [15]. Therefore, according to our hypothesis of the immune system disbalance and normalization, ascendancy therapy could be an analogue of SIT.

In this study, we analyzed the effect of ascendancy therapy with histamine in infectious allergic BA.

METHOD

The study involved 14 patients with moderate BA associated with chronic obstructive bronchitis. The disease record varied from two to five years.

We determined the total IgE in the blood by ELISA with a commercial kit (Khema-Medika, Russia). Antibodies to a wide range of pollen, household, food, and fungal antigens were assayed using a Top Screen ELISA panel (DIAPLUS, Switzerland–Russia). At regular intervals, we determined a complete peripheral blood immunogram including standard blood count, lymphocyte phenotyping by the streptavidin–biotin method with a DAKO kit (Denmark), determination of the endogenous intoxication of the organism (quantitation of the apoptosis antigen on the surface of cells, assessment of signs of degeneration in the nucleus and cytoplasm of leukocytes, determination of the phagocyte activity of neutrophils), and integral assessment of the immune system functioning with the load index (LI) [5].

We assessed the number of eosinophils and neutrophils in sputum of patients by microscopic examination of sputum smears stained with hematoxylin–eosin [16].

To monitor the effect of therapy, we used a test for leukocyte migration to the oral cavity [17].

Before treatment with histamine, all patients had frequent (occurring from four times a week to every day) bronchospasms at night and difficulty in breathing at a brisk walk. Objectively, the maximum expiratory flow rate increased by 27–38% after salbutamol inhalation. Physical load (squatting, 10 times) reduced the maximum expiratory flow rate by 45–50% or caused bronchospasm. The patients expectorated with difficulty a substantial amount of viscous sputum with jellylike clots, especially in the morning.

Immunograms of all patients showed a higher (5–8%) percent of eosinophils; the LI was reduced, suggesting a chronic process; and there were indications of stagnant inflammatory processes (a shift to the left in lymphocytes or neutrophils, a reduction of T cells, prevalence of T helpers among T cells) and endogenous intoxication (increased expression of Fas receptors on leukocytes, degenerative alterations in the nuclei and cytoplasm of leukocytes, a reduced phagocytic activity of neutrophils, or even hypogranulocytosis). There was a large amount of eosinophils in sputum smears of all patients.

All patients were subject to ascendancy therapy with histamine. Increasing doses of histamine were administered daily.

To prepare the therapeutic dilutions of histamine, we used commercial 0.1% histamine hydrochloride (Biomed). The dilutions were prepared with sterile saline (0.9% NaCl). The original solution was used as the first dilution; the second one contained 0.01% ($1 \times 10^{-2}\%$) histamine; in total, at least 12 tenfold dilutions were obtained. Solutions with intermediate concentrations were prepared from the basic solutions (e.g., 0.3×10^{-7} histamine was obtained by mixing 0.3 ml of $1 \times 10^{-7}\%$ histamine and 0.7 ml of saline).

As a carrier of histamine solutions, we used lignine disks (diameter 10 mm, thickness 3 mm), which were prepared with a special device and standard medical Cellulon tents (Hartmann). A disk absorbed 0.5 ml of liquid. A lignine disk was soaked with a histamine solution of a necessary concentration and put into the post-cheek space at the lower jaw for 1 h. Before and after application of a disk with histamine, we counted granulocytes in the washing fluid of the oral cavity, and the ratio of the two counts was determined [17].

The control group comprised 12 healthy volunteers, member staff and postgraduate students of the laboratory. The effects of immunomodulators and histamine on leukocytes and their migration into the oral cavity were established.

Statistical analysis of the data employed standard statistical methods. We calculated mean values and assessed the significance of differences between the means with the *t*- and Mann–Whitney nonparametric tests. All computations were done using the Statistica software.

RESULTS AND DISCUSSION

Three times, every other day, we determined the immunogram of the peripheral blood for nine healthy volunteers (aged 24–50 years) to obtain individual normal ranges.

After two days, three subjects (group 1) were intracutaneously injected in the lateral region of the arm with 0.5 ml of 0.1% histamine hydrochloride; injections were performed once a day for two days. Three other subjects (group 2) were similarly intramuscularly

Table 1. Changes in the immunogram parameters after two-day administration of immunomodulators or histamine

Time	Drug	Immunogram parameter						
		Leu, 10 ⁹ /l	Lym, %	N, %	E, %	M, %	T cells, %	LI
1st day	Before drug administration (control)	100 ± 2.7	100 ± 3.2	100 ± 3.7	100 ± 4.4	100 ± 2.1	100 ± 4.2	100 ± 1.9
	Taktivin	127 ± 6.4*	71 ± 10.7*	130 ± 9.8*	57 ± 5.9**	90 ± 5.8	75 ± 4.8**	140 ± 8.7**
	Bronchomunal	132 ± 8.6**	68 ± 11.3**	128 ± 7.6*	42 ± 6.1**	110 ± 6.1	80 ± 5.0*	127 ± 6.4*
2nd day	Histamine	139 ± 11.2*	60 ± 12.1**	134 ± 8.2*	60 ± 7.1**	122 ± 6.9	79 ± 3.2**	135 ± 7.7**
	Taktivin	119 ± 7.1*	98 ± 9.5	110 ± 5.9	65 ± 5.1**	91 ± 4.2	81 ± 5.4*	140 ± 9.1**
	Bronchomunal	123 ± 8.3*	102 ± 11.4	113 ± 6.2	50 ± 6.7**	109 ± 5.1	83 ± 3.9*	135 ± 7.2*
5th day	Histamine	118 ± 6.2	105 ± 9.9	105 ± 5.6	64 ± 5.9**	100 ± 3.9	76 ± 3.8*	132 ± 6.5*
	Taktivin	102 ± 3.6	120 ± 9.5	92 ± 4.9	107 ± 7.7	150 ± 4.9**	95 ± 3.1	108 ± 4.9
	Bronchomunal	97 ± 4.2	125 ± 10.0*	101 ± 5.1	100 ± 6.8	121 ± 6.1*	91 ± 4.2	98 ± 5.1
	Histamine	101 ± 2.9	110 ± 11.2	98 ± 3.8	93 ± 5.7	135 ± 4.8**	102 ± 3.8	102 ± 4.8

Note: Because the immunogram parameters substantially differed among the subjects before drug administration, which is common in healthy subjects [5], comparisons of the shifts for different groups were performed with relative values, taking the value observed before administration as 100%. Here and in Table 2: differences were significant at (*) $P \leq 0.05$ or (**) $P \leq 0.001$.

injected with 1 ml of 0.01% taktivin. The remaining three subjects (group 3) were administered bronchomunal *per os* at one capsule per day for two days. One, two, and three days after the last administration, we determined the immunograms for all subjects.

Administration of histamine caused local reddening, edema, and heat, which disappeared after 15–20 min. No clinical signs were observed after administration of taktivin or bronchomunal.

The results of laboratory tests are presented in Table 1 (we included only those parameters that showed significant changes). Immunograms of the subjects of all three groups displayed basically similar shifts from the initial data. An increased leukocyte count, which was due to an increased neutrophil count, was noted one day after drug administration; at the second day, it was due to a higher lymphocyte count. The percents of eosinophils and T cells decreased in the first two days and were normalized at the third day after drug administration. The LI was reduced throughout the three-day period.

The above shifts in the immunogram are characteristic of a subclinical inflammatory response of the organism. A similar response has been described for patients with chronic inflammatory processes after administration of various immunostimulators, such as taktivin, and immunostimulant antigen preparations, such as bronchomunal [4–6].

It was found that histamine brings about a similar reaction of the organism. Such shifts after administration of histamine were noted as early as in the 1940s and 1950s [18, 19]. Currently, the activating or suppressing effects of histamine are known for almost all cells of the immune system and are mediated by receptors on their membranes and activation of the cytokine

system. This indicates that histamine is a factor regulating the immune response and, therefore, the inflammatory response of the whole organism rather than affecting only the initial vascular and chemotactic responses [15]. These data may explain the shifts observed in the immunogram, pointing to activation of the inflammatory response after administration of histamine.

Because sublingual and subnasal administration of drugs are less traumatic and safer and, consequently, are commonly preferred over subcutaneous injection in specific or nonspecific hyposensibilization [20], we tested oral administration with the volunteers [17]. A lignine disk was impregnated with a solution of a required concentration and then placed onto the lower cheek area of the oral cavity for 60 min.

As follows from Table 2, after the application of a lignine disk with immunomodulator (taktivin), immunostimulator (imudon), or histamine, migration of neutrophils into the oral cavity substantially increased and their phagocytic activity grew higher. This again supports the above data that administration of histamine

Table 2. Measurement of the migration of neutrophils to the oral cavity and their phagocytic activity after application of lignine disks impregnated with drug solutions in the cheek area of the oral cavity for 1 h

Drug	Relative change in neutrophil count	Relative change in phagocytic activity
	% of the initial value	
Imudon	240 ± 27**	134 ± 9*
Taktivin	190 ± 19**	126 ± 7*
Histamine, $1 \times 10^{-7}\%$	270 ± 22**	129 ± 9*

Table 3. Changes in clinical characteristics in BA patients during ascendancy therapy with histamine

Parameter	Before therapy	After 20 days	After 30 days	After 3 months	After 6 months	After 12 months
Number of administrations of short-effect β -agonists required	Several times daily	Once daily	2–3 times a week, mostly at night	1–2 times a month	–	–
Increase in maximum expiratory flow rate after inhalation of salbutamol, %	29–49	15–35	5–15	0–10	0–10	0–10
Effect of physical load (squatting, 10 times)	Bronchial spasm	Bronchial spasm or difficulty in breathing	Difficulty in breathing	Alteration of expiratory flow rate upon forced exhalation	No changes	No changes
Jellylike clots in sputum	Several per day	Few	Absent	Absent	Absent	Absent

activates the immune system like administration of immunomodulators. In addition, we concluded that the test for changes in leukocyte migration into the oral cavity as a consequence of drug administration by our method is efficient and convenient for constant monitoring of the organism's reaction to the drug.

Thus, as we noted above, all our BA patients were subjected to clinical and laboratory inspection. Because all individuals had severe chronic intoxication of the organism, they were first subjected to detoxification (administration of an enterosorbent, preferably enterogel, two times a day between meals) for 10–15 days. After this course, repeated immunogram analysis revealed a substantial reduction or even complete elimination of the laboratory signs of intoxication; clinical symptoms of intoxication also became undetectable in all patients.

A course of ascendancy therapy with histamine began only after detoxification. A lignine disk was impregnated with a histamine solution and placed in the lower cheek space for 60 min daily. Cells were washed out of the oral cavity before and after histamine appli-

cation. Granulocytes were counted in a Goryaev chamber under a microscope. For most patients, $1 \times 10^{-11}\%$ was the initial histamine concentration. When administration of the given dose of histamine did not increase the cell count (i.e., the cell count in the washing fluid increased by no more than 5%), the dose of histamine was increased by a factor of 3.

When we reached the histamine concentration that increased cell migration into the oral cavity, the same dose was applied repeatedly until it ceased to stimulate migration of granulocytes. Usually, one dose was administered for 2–3 days (Fig. 1). Then the dose was again increased by a factor of 3, and application continued until a lack of stimulation of granulocyte migration. The dose was increased to a maximum of $1 \times 10^{-4}\%$. This dose was considered a supportive dose and was applied once a week for the next three months and every second week later on. (When this paper was prepared, the total observation period was 14 months in three patients and 4–6 months in the others.)

In one of our patients, treatment started with a dose of $1 \times 10^{-7}\%$ histamine. After the first application, this dose caused a fourfold increase in granulocyte migration (Fig. 2). Repeated administration of this dose for the next 10 days always induced high stimulation of granulocyte migration into the oral cavity. Administration of this dose was cancelled. After a 7-day break, the patient was administered $1 \times 10^{-11}\%$ histamine, which did not stimulate granulocyte migration into the oral cavity. The first, 1.4-fold, increase in granulocyte migration was noted in this patient only when the dose of histamine increased to $1 \times 10^{-9}\%$. On the next day, this dose of histamine did not stimulate migration. A further increase in the histamine dose activated granulocyte migration, and activation ceased after 2–4 repeated administrations. That is, treatment of the patient followed the above scheme. It can be hypothesized that hyposensibilization via specific or nonspecific ascendancy therapy is partly efficient or inefficient when the initial dose of the drug is too high, causing a common hyperreaction of the immune system. A positive clinical effect was noted in all our patients. As early

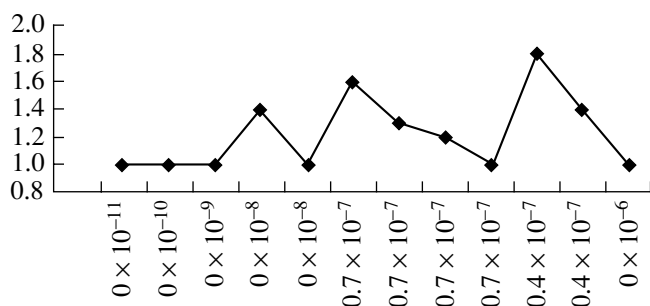


Fig. 1. An example of changes in granulocyte migration after daily 60-min application of a lignine disk with increasing concentrations of histamine in patient K. Abscissa, histamine concentration, %. Here and in Fig. 2: ordinate, changes in the count of granulocytes washed out from the oral cavity after the application of the lignine disk with histamine as compared with the count obtained before disk application.

as 20–30 days after the first histamine application, the patients clearly showed clinical and laboratory signs of transition to complete remission (Tables 3, 4). Remission became complete by the third month of supportive histamine therapy (one application in two weeks). Three out of the 14 patients were followed up for more than one year, and we did not observe laboratory or clinical indications of aggravation of the disorder.

All patients showed a gradual decrease in salbutamol-induced augmentation of the maximum expiratory flow rate, and the drop in the expiratory flow rate after physical load (squatting, 10 times) was reduced or disappeared. The need for β -agonists was reduced and later eliminated because no bronchial cramps took place. Morning expectoration of viscous sputum grew lower, and jellylike clots disappeared (Table 3).

Laboratory tests indicated that the eosinophil count normalized, as well as the level of T cells. Other signs of stagnant inflammatory processes became undetectable. The LI, which was initially low, increased (Table 4).

The course of curing certainly normalized the histamine release via some mechanisms, as also assumed by other researchers [14]. Yet normalization of histamine release was not the only cause because many researchers have not found a clear correlation of the growth of blocking antibodies and other factors stabilizing histamine release with the clinical picture of the disorder [2].

Furthermore, we noted a parallelism of the positive clinical effect of ascendancy therapy with histamine and normalization of the LI, which is an integral index of the immune system overstrain characteristic of any chronic inflammatory process. A lack of eosinophils in sputum and normalization of the eosinophil and T-cell counts in blood after cure point to normalization of several components of the immune system in the BA patients.

In addition to the above data showing that shifts characteristic of an inflammatory process take place in the immune system after administration of histamine at high doses, these findings make it possible to conclude that ascendancy therapy with histamine has a complex effect on the whole immune system in the case of

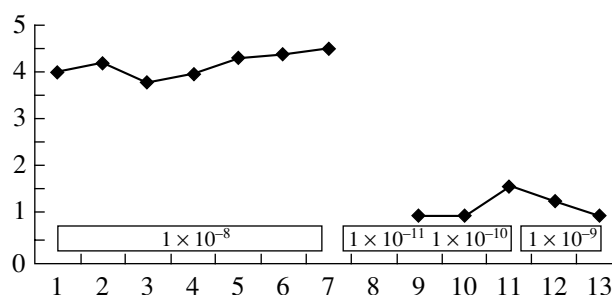


Fig. 2. Persistence of the hyperreaction of granulocyte migration to the oral cavity in patient F. on initial overdosage of histamine and its elimination after reduction of the starting concentration. Abscissa, days of histamine administration.

hyperreactive disbalance, directing the transition of the system to a normal functional balance.

CONCLUSIONS

Bronchial asthma is an example of a chronic disorder with hyperreactivity of certain components of the immune system. This hyperreactivity initiates the allergic responses and causes functional insufficiency of the immune system, bringing about chronic inflammation. Such disorders are probably a consequence of systemic disturbances of interactions between various components of the immune and other systems; i.e., the cause is disbalance at the level of a functional system. Disbalance in the immune system was previously proposed as the basis for every chronic disorder [3]. Yet many investigators consider this concept illusive because it is difficult to explain in terms of common routine tests. However, shifts in certain components of the immune system can be considered to reflect the overall disbalance in the system. The breakthrough in cytochemistry facilitated the discovery of many cytokines, which are involved in systemic interactions between components. However, even here there is no complete understanding of the interaction mechanisms.

The above systemic approach to functioning is promising, and many physiologists have formulated it in various ways. For example, Davydovskii [21], an outstanding physiologist, considered the problems of the norm and pathology from the viewpoint of adapta-

Table 4. Changes in laboratory characteristics of BA patients during ascendancy therapy with histamine

Measure	Before therapy	After 20 days	After 30 days	After 3 months	After 6 months	After 12 months
Eosinophils in sputum	+++	++	+	–	–	–
Blood eosinophils, %	4.8 (3–9)	4.2 (2–8)	3.4 (2–5)	2.7 (1–3)	2.5 (0–3)	2.8 (1–3)
LI	1.1 (0.6–1.4)	1.2 (0.7–1.4)	1.3 (0.9–1.6)	1.7 (1.4–1.9)	1.8 (1.6–2.1)	1.8 (1.7–2.0)

tion to the environment. Such adaptation may be due to alterations, often very significant, in certain components of the system. Clinically, such adaptation may develop within the limits of health in some individuals or as a disorder in some others. In either case, the major objective is to maintain the viability of the whole organism.

Let us consider the problems of BA treatment from this standpoint. As already noted, common BA treatment, including administration of drugs blocking particular components or cell receptors, is effective as long as drug administration continues. However, there is a therapeutic method that principally differs from all others. This is SIT. Gushchin [2] formulated the general conclusion that "SIT has a therapeutic effect that involves all components of the allergic process and is absent in the case of all known pharmacological preparations. SIT principally differs from pharmacological therapy in that its positive effect extends over a prolonged period after the end of treatment" [2]. We found an analogous pattern for ascendancy therapy with histamine in chronic allergy. In addition, dosed immunotherapy with immunomodulators and immunostimulators in chronic inflammatory processes is characterized by a similar effect [4].

In our opinion, the basis of such therapy is restoration of the balance of the immune system owing to its training in the normal mode. Using minimum doses of drugs, we cause minimum physiological activation of the immune system, which brings about a weak normal response of the organism. When such doses are used several times, the immune system adapts to the development of the normal response. Increasing doses of the drug activate the immune system at a new qualitative level, and the system is further adapted to function in the normal regime. Thus, the immune system is trained to work normally at the load that is provided for by the given activation, be it metabolic as with immunomodulators, antigenic as with microbial immunostimulators, allergenic as in SIT, or histamine as in ascendancy therapy. Most probably, such dosed training gradually reduces the disbalance in the immune system and restores its functioning to achieve the desired state, which is activation in chronic inflammatory disorders or reduction of hyperreactivity in chronic allergic disorders.

Thus, the above methods of therapy actually train the immune system to develop normal reactions and are effective in various chronic disorders. Unlike other methods, they make it possible to attain prolonged stable remission, if not complete cure, and to suppress further development of the pathological process. Yet these methods are not widespread because cure is observed only in some patients. We hypothesize that partial efficiency or inefficiency of these curing methods is associated with disruption of immune system adaptation to normal reactions to the drug.

Thus, for a stable clinical effect, it is most important to select the optimal starting doses of the drug and to control adaptation to increasing doses. We successfully used the LI, a systemic index reflecting the activity of the functioning of the immune system [5]. Yet the LI reflects the final result of the immune system response, which requires a while to develop and is thereby unsuitable for rapid adjustment of the drug dose. A simple and rapid test for granulocyte migration to the oral cavity allows the monitoring of the effect of continuous introduction of the drug via the mucous membrane of the oral cavity [17]. This test yields reliable information about the efficiency of each dose of the drug and allows rapid adjustment of the dose.

To conclude, the immune system, like other systems of the body, is complex and multicomponent. Chronic disorders are usually underlain by disturbances of systemic interactions rather than by changes in individual components. The situation is even more complicated when atypical responses of the system are involved. An example is provided by BA. It is clear and evident from clinical experience that treating such disorders by affecting a particular component is ineffective for the whole organism because continuous administration of a drug is needed to maintain the effect. It is possible to achieve real success in a cure only by restoration of the whole system [22]. However, this is difficult and requires accurate execution of the protocol and continuous monitoring of the drug effect.

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