

Late-phase inflammation: Influence on morbidity

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With the prevalence of asthma and other allergic diseases increasing, the question of late-phase inflammatory response, a dynamic inflammatory response to a single exposure to antigen, has come to the forefront as one possible explanation for this increase in morbidity. If this explanation is acceptable, clinicians must examine their methods of management of allergic diseases and shift from crisis intervention with β -agonists for asthma and first-generation antihistamines or decongestants for rhinitis to disease control with antiinflammatory agents. Topical application of corticosteroids to the upper airways blocks mediator release from the early and late phases after antigen challenges. In addition, recent studies using the skin-blister chamber model have shown that some of the newer, second-generation antihistamines may attenuate the infiltration and activation of eosinophils, neutrophils, and basophils during the late-phase response. Immunotherapy may have a selective effect, targeting inflammatory aspects of the late-phase response. It is clear that corticosteroids, second-generation antihistamines, and immunotherapy play a role in modifying the late-phase response and that each of these therapeutic modalities may operate by a different mechanism. (J Allergy Clin Immunol 1996;98:S291-7.)

Key words: Antihistamines, asthma, cetirizine, corticosteroids, late-phase response, misoprostol, terfenadine

The past two decades have witnessed a significant increase in the prevalence of and morbidity due to asthma in the United States and Europe. Whereas the prevalence of asthma increased by only 0.5% between 1928 and 1931, it rose by an estimated 29% from 1980 to 1987.¹ Furthermore, hospitalizations for childhood asthma increased by 200% between 1965 and 1983.² Of note, morbidity due to asthma is greater among black children than among white children; this morbidity appears to be disproportionate in the rising national morbidity. The reasons for the greater number of deaths due to asthma among black children are multifactorial and include fragmented medical care with lack of routine follow-up, poor inner-city conditions compounded by pollution and cockroach allergens, and inadequate focus on the late-phase inflammatory aspects of asthma.

The inflammatory aspects of the late-phase response (LPR) are one possible explanation for the observed increase in asthma morbidity worldwide. Studies of the mechanisms of the LPR suggest an association between increased asthma morbidity and failure to address the inflammatory aspects of allergic disease adequately. Treatment of the LPR may include the use of selected antihistamines, corticosteroids, cromolyn or nedocromil,

Abbreviations used

GM-CSF:	Granulocyte-macrophage colony-stimulating factor
HRF:	Histamine-releasing factor
LPR:	Late-phase response
LTC ₄ :	Leukotriene C ₄
PGD ₂ :	Prostaglandin D ₂
PAF:	Platelet-activating factor

and immunotherapy in a treatment program aimed at the late inflammatory events of the allergic reaction.

The LPR is a dynamic inflammatory response to a single exposure to antigen, resulting in an interplay of inflammatory cells and proinflammatory mediators and cytokines. Although clinicians have only recently begun to appreciate the significance of the LPR, it was first described in 1873 by Blackley,³ who described the development of upper- and lower-airway symptoms that evolved over a period of several hours after a single exposure to grass pollen. In 1922, Cooke⁴ tested his own reaction to horse dander intradermally and noted that, in addition to the expected wheal and flare usually seen in an allergic person, other symptoms, including local swelling, edema, and erythema, persisted for longer than a day. In the early 1950s, Herxheimer⁵ noted the clinical significance of the late bronchial reaction as a portent of asthma severity. A decade and a half later, Pepys et al.⁶

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described the cutaneous histologic LPR in response to *Aspergillus* skin testing; however, he mistakenly thought that this reaction represented a type III or Arthus reaction when, in reality, no true inflammation of the vessel wall had occurred.

In the mid-1970s, several groups of investigators⁷⁻⁹ established clearly that the LPR is IgE mediated and is dependent on an initial acute reaction to antigen. This initial reaction ushers in a complex cascade of inflammatory events that are still the target of intensive investigation. In 1976, Solley et al.⁸ demonstrated that immediate-phase responses and LPRs of the skin to antigen could be passively transferred to nonallergic volunteers. However, when the IgE was removed from the serum by an anti-IgE solid-phase immunosorbent, the cutaneous LPR was not passively transferred. Through these studies it was firmly established that the cutaneous LPR is mediated through the triggering of cutaneous mast cells, either by specific IgE or by anti-IgE. In 1985, Naclerio et al.¹⁰ showed that after nasal challenge with a single exposure to antigen, an initial release of histamine occurred, followed by a second release of histamine. The first but not the second release of histamine was accompanied by the release of mast cell-derived prostaglandin D₂ (PGD₂), a finding that suggested that the second release of histamine is caused by basophil infiltration, a hypothesis later confirmed by Bascom et al.¹¹ in the same laboratory.

Because the skin has been used to diagnose allergic disease for nearly a century, our group¹² used a skin-chamber model to confirm that the skin shows the same biphasic release of histamine as was shown with the nasal challenge. The histologic findings of the cutaneous LPR are characterized by an infiltrate comprising neutrophils, eosinophils, basophils, and lymphocytes. This infiltrate eventually changes to a monomorphous infiltrate consisting of CD4⁺ lymphocytes.¹³

In the diagnosis of allergic nasal and respiratory disease, skin-prick and intradermal tests are used to produce an immediate wheal-and-flare reaction to the injected antigen. In some allergic subjects, the immediate reaction is replaced by an LPR that peaks between 8 and 12 hours after injection. The rate of LPR in the skin varies from 20% to 85%, clearly rising with increasing concentrations of antigen used in skin testing.¹⁴⁻¹⁷

The importance of the skin as a model for the study of allergic disease has gained greater significance with the clinical observation that the LPR is frequently seen in patients with asthma or allergic rhinitis. The significance of the LPR was underscored by Warner et al.,¹⁸ who showed that in a group of house-dust-mite-allergic, asthmatic children, immunotherapy produced a marked attenuation of the LPR after antigen bronchoprovocation challenge. Several years later, Cockcroft et al.¹⁹ reported an increase in nonspecific bronchial hyperreactivity after antigen bronchoprovocation proportional to the intensity of LPR. Clearly, enhanced bronchial reactivity is the hallmark of asthma. If the pathophysiologic mechanisms responsible

for the late reactions observed in the skin are analogous to those observed clinically in the airways, then the skin model to study the cutaneous LPR assumes greater importance in the study of allergic diseases. The distinct association of the LPR with bronchial reactivity underscores the importance of research toward a better understanding of the underlying mechanisms of late inflammatory events.

AGENTS CAUSING A CUTANEOUS LPR

Several nonantigenic or nonimmunologic substances and stimuli have been reported to cause late cutaneous reactions similar to those described with antigens. Although histamine alone cannot induce LPR in the skin, compound 48/80, an agent that induces nonimmunologic mast-cell degranulation, has been shown to induce the LPR.²⁰

Leukotriene C₄ (LTC₄) and other products of the lipoxygenase pathway of arachidonic acid metabolism induce clinical and histologic skin lesions that resemble the LPR,²¹ whereas PGD₂, a product of the mast-cell cyclooxygenase pathway of arachidonic acid metabolism, does not produce a cutaneous LPR. In addition, intradermal injection of platelet-activating factor (PAF) results in dermal histologic features identical to those occurring in the cutaneous LPR.²² Further clinical relevance of the action of PAF is suggested by the demonstration that PAF selectively induces an eosinophilic dermal infiltrate in allergic but not nonallergic subjects.²³ PAF also produces a prolonged increase in bronchial hyperresponsiveness. Hargreave et al.²⁴ have noted an association between the degree of bronchial hyperresponsiveness and the intensity of the LPR, perhaps mediated in part by PAF. Weiss et al.²⁵ reported that a histamine-releasing factor (HRF) derived from platelets can also induce an LPR. It remains to be seen whether the agents reported to cause a cutaneous LPR do so by similar mechanisms. There may be multiple operative mechanisms by which the skin and the airway exhibit biphasic inflammatory responses, and these differences may explain why a single inflammatory cell or a single mediator has not been identified as the critical factor in the development of the LPR.

INFLAMMATORY MEDIATORS OF THE LPR

A plethora of mediators produced or released by inflammatory cells after antigen stimulation in allergic subjects have been described (Table I). This discussion focuses on a few of these mediators.

Zweiman et al.²⁷ demonstrated a rapid increase in histamine into the skin chamber; the level peaked by 30 minutes and declined during the subsequent 4 hours. The total amount of histamine released during this initial phase correlated significantly with the intensity of the subsequent LPR as measured by skin testing.²⁷ Shalit et al.²⁸ reasoning that natural exposure to antigen in allergic subjects occurs over a protracted period of hours or days, examined mediator release after a continuous antigen challenge. Histamine and mast-cell-derived

tryptase were abruptly released in response to the continuous antigen challenge; this response was followed by a complete return to baseline values of the level of tryptase but not that of histamine. Histamine was continuously released over the 6-hour observation period. Because the level of tryptase, a mediator released upon mast-cell degranulation, declined, one possible source of the persistent presence of histamine may be the peripheral-blood basophil, which contains no significant tryptase and which is present in the LPR. An alternative explanation may be that there is more than one mechanism for the release of histamine and tryptase from mast cells.

Using the skin chamber model to study the LPR for an extended, 12-hour period, we have observed a second rise in histamine, analogous to that reported in the airways.²⁹ There was an initial peak of histamine (13.2 ± 2.9 ng/ml) into the chamber during the first hour, but the level declined to approximately 2 ng/ml during the next 6 hours. This decline was followed by a slow, persistent rise that culminated in the release of almost 10 ng/ml of histamine during the twelfth hour. Subsequent experiments have shown that this second rise in histamine usually peaks at hour 11 or 12 and is followed by a slow decline to baseline. The difference in time kinetics between the early and the late histamine release suggests that the basophil, rather than the mast cell, may be the source of this late appearance of histamine. However, it is also possible that both mast cells and basophils make a contribution to the increased levels of histamine noted during the cutaneous late phase. The production of PGD₂ during the early-phase response but not the LPR lends support to the hypothesis that the late-phase histamine originates from the basophil, which does not produce PGD₂.

Slow-reacting substance of anaphylaxis, which is now recognized to comprise sulfidopeptide leukotrienes including LTC₄, has been of interest to allergists for a number of years. Using the skin chamber model, Talbot et al.³⁰ showed that LTC₄ was released in response to an antigen challenge and that peak LTC₄ concentrations occur between the second and fourth hours after antigen challenge. In their study, the time kinetics of LTC₄ production varied considerably among subjects without predictable peaks or patterns of release of either histamine or PGD₂.

We recently examined LTC₄ production in response to antigen, noting both early-phase and late-phase elevations in production; however, a marked intrasubject variability occurred.³¹ Furthermore, when subjects were treated with prednisone 60 mg for 3 days preceding the study, LTC₄ production was significantly suppressed, correlating with the suppression of eosinophils by corticosteroids. We concluded that most of the LTC₄ recovered from late-phase blister fluid emanated from eosinophils. Certainly, leukotrienes may be important in the LPR in asthma because of their ability, in very small amounts, to cause bronchoconstriction. Production of LTC₄ by activated eosinophils, in concert with other mediators, probably contribute significantly to the clinical LPR.

Release of leukotriene B₄ into the skin chambers in

TABLE I. Mediators and inflammatory cells

	Immediate response	Late response
Mediators	Histamine TAME-esterase Kinin PGD ₂ Leukotrienes C ₄ , D ₄ , E ₄ Leukotriene B ₄ Tryptase PAF MBP EDN	Histamine TAME-esterase Kinins Eosinophil cationic protein MBP EDN
Cells	Eosinophils	Eosinophils Neutrophils Mononuclear cells Basophils Epithelial cells

EDN, Eosinophil-derived neurotoxin; MBP, major basic protein.

response to a single antigen challenge has not been demonstrated. However, leukotriene B₄ can be detected in skin chambers challenged with a continuous low dose of antigen, again suggesting that different mechanisms may be involved in these two challenge models.³² The pattern of mediator release detected in the skin chamber may not fully reflect the kinetics of local tissue production, and very small concentrations of a given mediator may have a profound effect on the local tissue milieu immediately surrounding the site of mediator production.

An interesting mediator, and one that may play a critical role in the LPR response, is PAF. The presence of PAF was recorded in the skin chambers of 74% of allergic subjects who were given a continuous low-dose antigen challenge. PAF was initially detected during the third hour and persisted for 9 hours after antigen challenge.³² PAF can cause release of LTC₄ from eosinophils and is one of the most potent known chemotactic factors for eosinophils.³³ Because eosinophils have low-affinity receptors for IgE, it is conceivable that antigen may activate eosinophils through this low-affinity receptor and cause the production and release of PAF into the surrounding tissues.

Fibrin has been described as a component of the cutaneous LPR. Both thrombin and collagen have been shown to release PAF from platelets.³⁴ Whereas it is known that human lung mast cells can produce PAF, production of PAF by the cutaneous mast cell is still under investigation. Chilton and Connell³⁵ demonstrated that the metabolism of PAF is intricately involved with the arachidonic acid pathway, providing further evidence of a link between PAF metabolism and the cyclooxygenase and lipoxygenase pathways. Clearly, PAF is a major component in the LPR, resulting in in-

creased vascular permeability, increased tissue edema, and enhanced eosinophil diapedesis.³⁶

A myriad of other mediators probably are involved in the LPR in the skin and the airways. Cytokines in particular may prove pivotal to a better understanding of the LPR. Bochner et al.³⁷ used bioassay and immunoassay to show that IL-1 (IL- β) is increased in late-phase skin-blister fluids. Although its exact place in the cutaneous LPR is uncertain, the many biologic properties of IL-1 could intensify the LPR. IL-1 stimulates the adherence of leukocytes to vascular endothelium by the induction of specific surface proteins such as endothelial leukocyte adherence molecule-1.^{38,39} Stimulation of endothelial cells by IL-1 promotes the adherence of eosinophils, basophils, and neutrophils, all of which are associated with the LPR. Although IL-1 is produced primarily by mononuclear cells, many other cell types observed histologically in the LPR can also produce this cytokine. Initial evidence that IL-1 may enhance basophil histamine release has been found by several groups. This activity of IL-1 may explain observations of increased histamine in late-phase skin-chamber studies.^{40,41} It is tempting to speculate that corticosteroids, which are known to be specific for the late but not the early phase of the allergic reaction, act by blocking IL-1 production because they inhibit both the LPR and IL-1 production. It is probable, however, that several cytokines contribute to the complex sequence of events in the LPR.

Another class of mediator that may contribute significantly to LPR events was first described by Thuesen et al.⁴² in 1979 and named HRF because of its ability to enhance histamine release. Although HRF was first described in association with human monocytes, several cell types were later shown to release factors that induce histamine release. The presence of HRF has been demonstrated in late-phase skin chamber fluid.⁴³ Additional studies suggest that HRF may be dependent on the presence of a unique IgE^{44,45} and that the presence of this IgE may distinguish atopic from nonatopic subjects. This finding has led to the hypothesis of IgE heterogeneity, in which the IgE from certain responders would have high affinity to bind HRF and an LPR is more likely to develop in these patients. This association is given further credence because both HRF and basophils are present in late-phase skin-blister fluids coincident with the late release of histamine. In the airway, the intensity of the LPR correlates with the responsiveness of the donor's basophils to HRF. Nevertheless, the concept of HRFs is complex, and there are probably several IgE-dependent and IgE-independent HRFs. A complete understanding will depend on purification, cloning, and further characterization of these various HRFs.

In summary, when the IgE attached to the skin mast cell is bridged by antigen, a transmembrane signal ultimately results in the release of preformed mediators and the production of newly synthesized mediators. Within 30 minutes, a maximum amount of histamine can be recovered from the skin chamber. Other mediators, such as PAF, functioning as a potent chemoattractant for eosinophils, are synthesized and contribute to the production of

the LPR. HRFs produced and released into the skin blister fluid then augment the release of histamine from the infiltrating basophils. Neutrophils, appearing as early as the fifth hour after allergen challenge, release various proteases and superoxides. The activated mononuclear cells release IL-1, which up-regulates the late inflammatory events and may contribute to the increased ability of basophils to release histamine.

Other cytokines may have a role in the genesis of LPR. Our group⁴⁶ has identified several cytokines in skin-blister fluid during LPR, including IL-6, IL-8, and tumor necrosis factor- α , in addition to IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF), which activate the eosinophil and promote its survival. The events leading to the LPR are intricate and interdependent. In the past, some investigators have favored one particular inflammatory cell or mediator as the critical factor necessary for late-phase induction; however, it is now apparent that the clinical LPR consists of events dictated and orchestrated by several cells and inflammatory mediators.

THERAPEUTIC IMPLICATIONS OF THE LPR

If the premise that the LPR accounts for some of the observed increase in asthma morbidity and mortality during the past two decades is accepted, it becomes evident that the focus of clinicians must shift from mere crisis intervention with β -agonists to disease management with antiinflammatory medications and nonpharmacologic modulation of the LPR.

Although glucocorticoids have little or no effect on the acute wheal-and-flare response to cutaneous antigen challenge, they do inhibit the LPR.⁴⁷ This feature has been demonstrated in the lungs, the upper airways, and the skin.⁴⁸⁻⁵⁰ Topical application of corticosteroids to the upper airways blocks mediator release from the early and late phases after antigen challenges, whereas systemic administration of corticosteroids block only the LPR.⁵¹ Using a skin-chamber model, our group examined the effect of 3 days of pretreatment with prednisone 60 mg/day on cellular infiltration and mediator release in allergic subjects.²⁹ Pretreatment with prednisone did not eliminate the immediate skin erythema or release of histamine but did eliminate the late secondary erythema and late histamine release. The reduction in histamine release during the LPR consequent to therapy with corticosteroids correlates with an almost total elimination of eosinophilic and basophilic migration during the LPR. The effects of systemic steroids appear to be specific to the eosinophil and the basophil, because the number of neutrophils in the peripheral blood and in the skin chambers has been found to increase during the LPR of corticosteroid-treated subjects.⁵¹ Systemic corticosteroids inhibit the synthesis of cytokines that are responsible for eosinophil activation and their adhesion to the vascular endothelium.

Topical corticosteroids applied to the target mucous membrane have the added benefit of decreasing mast-

cell number and releasability after only a week of pretreatment. With the use of topical steroids delivered to the airways, side effects associated with systemic steroids are now minimized and relief of LPR-associated symptoms is attained.

Recent evidence suggests that some of the newer, second-generation antihistamines may have effects that cannot be explained solely on the basis of histamine H₁-receptor blockade. Several of these drugs inhibit the release of histamine and leukotrienes *in vitro* and at pharmacologic concentrations *in vivo*. With recognition of the importance of the late cellular events in allergic disease, there has been increased interest in antihistamines that may attenuate the infiltration and activation of inflammatory cells during the LPR.^{52,53} Using the skin-chamber model, Massey et al.⁵⁴ examined the effects of terfenadine on the LPR. Terfenadine significantly inhibited the size of the cutaneous reaction at every hour from hours 1 through 9. Although terfenadine blocked histamine release after nasal antigen challenge, histamine release at skin-blister sites was unaffected.

Our group extended the examination of the newer H₁-receptor blockers to include cetirizine, promethazine, and chlorpheniramine.⁵⁵ All three antihistamines decreased the immediate and early skin-test reactivity to antigen. However, only cetirizine significantly decreased late leukocyte migration into antigen-challenged chambers, with a 68% reduction in eosinophils; neutrophils and basophils decreased similarly. In contrast, promethazine and chlorpheniramine induced no significant alteration in inflammatory cell infiltration. These results confirm previous observations that the influx of eosinophils into the skin is blocked by cetirizine many hours after antigen administration.⁵⁶ In comparison with the effects of corticosteroids, which selectively blocked eosinophil and basophil infiltration into the skin, cetirizine decreased infiltration of all cellular types.

Prostaglandins have been implicated in the pathogenesis of inflammation. These arachidonic acid metabolites have proinflammatory effects and antiinflammatory properties. PGD₂, a known mast-cell product, has potent bronchoconstricting properties, whereas prostaglandin E₂ is a strong smooth-muscle relaxant capable of inhibiting the activation of neutrophils, basophils, and monocytes. Alam et al.⁵⁷ studied the effect of misoprostol, a prostaglandin E analog approved for clinical use in the prevention of gastroduodenal ulcers caused by nonsteroidal antiinflammatory drugs, on allergen-induced cutaneous immediate and late-phase allergic reactions. Misoprostol significantly inhibited eosinophil chemotaxis and the production of GM-CSF. It also selectively inhibited the LPR but not the immediate-phase response. The observed antiallergic properties of this agent may have profound clinical implications if these results are duplicated by other investigators.

Immunotherapy is another therapeutic approach to the LPR. In a controlled prospective study, Fling et al.⁵⁸

demonstrated a decrease in the cutaneous LPR in a group of mountain-cedar-allergic subjects given immunotherapy, suggesting that immunotherapy may have a selective effect on the LPR.

In collaboration with Leiferman and associates, we⁵⁹ studied the effect of immunotherapy on the LPR by measuring early and late histamine and skin-test reactivity in the skin-blister-chamber model. In this study, the ability of late-phase skin-chamber fluids to support eosinophil viability at 96 hours was used as an indirect measure of the biologic activity of IL-3, IL-5, and GM-CSF. Our results, thus far unique, show that immunotherapy decreased early and late histamine and markedly attenuated late-phase skin-test reactivity. Results of assays using a series of monoclonal antibodies directed against IL-3, IL-5, and GM-CSF showed that immunotherapy blocked the release of IL-3 and GM-CSF into the chamber fluids.

Because these cytokines are responsible for promoting eosinophil viability and activation, it may be hypothesized that immunotherapy may decrease the deleterious effects of eosinophils while suppressing both early and late histamine release. Immunotherapy may thus decrease the inflammatory events observed during the LPR.

In summary, complex inflammatory events are associated with the LPR. An explanation for the increasing morbidity due to asthma may be inadequate attention from clinicians to the inflammatory aspects of allergic disease. Corticosteroids may modulate the LPR. Selective second-generation antihistamines also may decrease the LPR. Other medications, which modulate events related to the activity of arachidonic acid metabolites, also may affect the LPR. Immunotherapy may affect the LPR by altering late inflammatory responses. The focus of allergy treatment in the future will probably shift from treatment of the immediate phase of the allergic reaction to therapy for the inflammatory aspects of the LPR.

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Changing concepts of allergic disease: The attempt to keep up with real changes in lifestyles

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In the past 100 years, changes have occurred in the outdoor environment and in houses that have contributed to the increased prevalence of hay fever and asthma. Much evidence indicates that exposure to indoor allergens is an important cause of asthma. Changes in housing that have contributed to the increased prevalence and severity of asthma include increased temperature, decreased ventilation, and permanent carpeting. In addition to these changes, geographic differences in allergens, deficiencies in cleanliness, poor health care, passive smoke, and lack of exercise also contribute to the increase in severity of asthma that

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