

THE LATE PHASE SKIN REACTION: PARADIGM OR EPIPHENOMENA?

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Introduction

PHYSICIANS INVOLVED in the management of allergic diseases have traditionally thought of allergy in terms of acute symptomatology manifesting itself shortly after exposure to allergen. Such allergic reactions are exemplified by the wheal and flare induced by intradermal injection of histamine, a major mediator of so-called immediate hypersensitivity. This inflammatory response appears within minutes and resolves within an hour. To the contrary, as recently discussed, early students of allergy noted that clinical allergic reactions were frequently longer in duration.¹ In 1873 Blackley reported that he developed upper and lower respiratory tract symptoms which evolved over hours following an accidental inhalation of a large quantity of grass pollen to which he was allergic. The reaction was severe enough to cause his absence from work for two days.² Eighty years elapsed, however, before Herxheimer suggested that late asthmatic reactions might be as important as immediate ones,³ and almost a century more before the work of Pepys and colleagues with industrial enzymes and *Aspergillus* stirred the present interest in these late onset responses.^{4,5} At about the same time work in the Netherlands with house dust allergic asthmatic children showed that this common environmental allergen induced late asthmatic reactions in half of those exposed by bronchial challenge.⁶ Soon ragweed was similarly incriminated.⁷

Clues that dermal reactions to histamine represented only part of the allergic response were also present early on. In 1922 Cooke described biphasic dermal reactions to horse dander where an immediate WFR evolved into an area of swelling and redness which lasted for 24 hours.⁸ Biphasic dermal reactions to *Aspergillus*

species⁹ and *Bacillus subtilis*¹⁰ were reported almost 50 years later. It soon became apparent that the study of these dermal reactions might provide information concerning the immunopathogenesis and treatment of allergic disease manifested in other organs. Are biphasic dermal reactions a useful paradigm for the study of systemic allergic reactions with a late time course in man? We will address this question in the following paragraphs.

Types of Late Onset Dermal Reactions in Man

Four major types of late onset dermal reactions to injected antigen have been described in man (Table I). Classical delayed hypersensitivity reactions (DH) like those seen to tuberculin begin as local itching at the site of antigen deposition around 12 hours after intradermal injection. They subsequently develop into areas of local induration which may be painful if large, and which peak in severity between 24 and 48 hours and then resolve. Recent studies have shown that in addition to mononuclear cell infiltrates these reactions are characterized by infiltration and degranulation of basophilic leukocytes, degranulation and replication of fixed tissue mast cells, increased vascular permeability with dermal and epidermal edema, and activation of the clotting system with deposition of fibrin in a characteristic intervascular pattern in the reticular dermis.¹¹ The polymerization of extravascular fibrogen in these reactions forms a gel-like structure of trapped tissue fluids producing prominent, clinically detectable induration.

Similarly timed reactions can be induced in man and animals without exposure to mycobacterial proteins by intradermal sensitization with heterologous proteins and are called cutaneous basophil hypersensitivity (CBH).¹² Resulting reactions are first detectable at 12 hours and reach maximal intensity at 24 to 72 hours. They are pruritic but are less intense, less prolonged and more evanescent than DH reactions. When individuals are repeatedly rechallenged with antigen (such as keyhole limpet hemocyanin) apparent CBH reactions become biphasic. In that setting immediate wheal and flare reactions develop which disappear in 30-60

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Table I. Types of Late Onset Dermal Reactions in Man

1. Delayed hypersensitivity reactions*
2. Cutaneous basophil hypersensitivity*
3. Arthus reactions*
4. Late phase reactions†

* May be associated with wheal and flare reactions which may or may not play a role in induction of the late onset reaction.

† Biphasic with initial wheal and flare reaction.

minutes, while associated late reactions become less intense and of shorter duration.¹³ The late phase of CBH reactions in guinea pigs is characterized by dense accumulations of basophils of a degree not seen in delayed hypersensitivity reactions and only scant accumulation of fibrin. The exact significance of these reactions in man is unclear, although basophil infiltration has been reported in renal allograft rejection and allergic contact dermatitis in man.¹⁴

Arthus reactions are characterized histologically by local vasculitis at the site of antigen injection with an acute inflammatory infiltrate of neutrophils, vascular damage and endothelial proliferation, and the involvement of host immunoreactants such as immunoglobulin and complement. Fibrin is present but is preferentially localized to vascular and perivascular areas that are spared in delayed type reactions.¹⁵ Arthus reactions are uncommon in man although they have been reported to occur following tetanus toxoid injection and in a minority of diabetics with local reactions to insulin.¹⁶ In the diabetic patient local pain, erythema and induration peaked at 6–12 hours after intradermal testing with insulin and was not preceded by a wheal and flare reaction. In the Arthus-type dermal reaction reported to aspergillus in patients with allergic bronchopulmonary aspergillosis dual (WFR-Arthus) reactions occurred,⁹ and thus form a second type of biphasic dermal reaction in man.

A fourth type of biphasic reaction is the late phase reaction, also termed the late cutaneous allergic response.¹⁰ After the wheal and flare reaction to intradermally injected allergen peaks at 15–30 minutes inflammation begins to dissipate, but never completely resolves. Three to four hours later the dormant lesion becomes pruritic and painful to touch, warm, erythematous and edematous. Large lesions have well circumscribed borders. This local reaction then develops into a prominent lesion usually fully manifest at 6–12 hours. With large antigen doses LPR may continue to increase in size for up to 24 hours. Reactions persist for up to 48 hours and may be associated with considerable discomfort with soreness and pain to touch.

Although the different timing and appearance of these four types of reactions provides clues which facilitate their identification, histopathological studies are necessary for confirmation and elucidation of their pathogenesis. For instance, we have found that three different types of local reactions may occur to one

Table II. Features of Late Phase Reactions

- IgE/Mast cell dependent
- Evoked by anti-IgE
- Transferred in heat sensitive P-K test
- Produced by any antigen producing WFR
- Produced by Compound 48-80
- Transferred by blister fluid from 30–60 minute LPR
- Refractory period of 7–21 days

antigen: insulin (LPR, DH, Arthus).¹⁶ The appearance and time to peak response to dermal reactions may be altered by the frequency and quantity of allergen injection. Thus clinical identification of dermal reactions on clinical grounds can lead to erroneous diagnosis.

Features of Late Phase Reactions

Several unique features of LPR are summarized in Table II. First, a number of studies have demonstrated that the reaction is IgE and mast-cell dependent. It is evoked by dermal injection of anti-IgE antibody,¹⁷ transferred in the Prausnitz-Küstner (PK) test,^{17,18,19} prevented by absorption of IgE from the PK serum,¹⁸ produced by any antigen capable of eliciting a WFR, and reproduced by injection of the non-specific mast cell degranulator, Compound 48-80.^{18,19} The size of the LPR is directly related to the size of the WFR^{1, 18, 19} with WFR as small as 9.1 ± 1.0 mm in diameter inducing LPR.¹⁹ Unlike the flare of the WFR the LPR occurs independently of sensory innervation.¹

Late phase reactions can be produced by injection of blister fluid obtained from developing LPR at 30–60 minutes, but blister fluids obtained later produce only weak reactions.²⁰ Thus the short-lived depletable mediators responsible for production of LPR appear to be present in fluid-phase materials available for study. Furthermore, there is a "refractory period" of 7–21 days during which injection of allergen into the site of a previous LPR elicits a reduced response.²¹

Pharmacologic Modulation of the LPR

The effect of drugs on the LPR is summarized in Table III. The effects of oral H1 and H2 antagonists alone or in combination have been extensively investigated in one study.²² Although an H1 antagonist decreased the size of the WFR, a result not noted with an H2 antagonist, neither the H1 nor H2 antagonist influenced the LPR when administered alone. However, the combination of both types of antihistamines given simultaneously not only suppressed the WFR greater than the H1 antagonist alone, but almost completely blocked the development of the LPR. This finding was surprising in view of our earlier investigations which failed to demonstrate a modulatory role of histamine on the LPR¹⁹ and requires further investigation. Administration of potent steroid preparations orally or locally at the time of allergen injection reduces the size of the LPR by at least 50%.^{23,24} The β_2 -agonist, terbutaline, has been reported to have no²⁵ or small inhibitory effects on the LPR.²⁴ The prostaglandin synthetase

Table III. Reported Pharmacologic Modulation of Late Phase Reactions*

	No effect	Mild suppression	Blocked
Antihistamines	Chlorpheniramine ²² Cimetadine ²²	Clemastine ²⁸	Chlorpheniramine with cimetadine ²²
B ₂ agonists	Oral terbutaline ²⁵	Local terbutaline ²⁴	—
Prostaglandin-synthetase inhibitors	ASA ²² Topical indomethacin (5%) ²⁶	—	—
Corticosteroids	—	—	Prednisone ²³ Betamethazone ²⁴
Chromolyn-like drugs	Lodoxamine ²⁷	Ketotifen ¹⁸	—

* Superscripts refer to citations in the reference list.

inhibitor, indomethacin, applied as a 5% CREAM,²⁶ had no significant effect on the size of the LPR. Some decrease in associated erythema was noted. The systemically absorbed cromolyn-like drug, lodoxamine, which is capable of blocking late asthmatic reactions, has been reported not to block LPR,²⁷ although another cromolyn-like drug, ketotifen, produced some inhibition.²⁸

Histopathology of LPR

Several investigators have studied the histopathology of LPR.^{17,18,19,29,30} Our own studies evaluated LPR induced directly or in PK sites injected with ragweed and in LPR induced with Compound 48-80. Results were compared with those of ragweed injected sites which manifested WFR but no LPR.¹⁹ This last important control had not been performed in earlier studies of six hour reactions. Histopathological evaluation of 1 μ m Giemsa stained sections of LPR showed a relatively sparse mixed cellular infiltrate in which mononuclear cells were predominant. Polymorphonuclear leukocytes, eosinophils, and degranulated basophils and mast cells were present, but in small numbers. The cellular infiltrate of the six hour LPR was not distinguishable from control sites of isolated WFR (Figure 1). Sites of LPR were distinguished at six hours from those of isolated WFR, however, by the presence of the substantial fibrin deposits previously mentioned. Immunofluorescence studies confirmed the results of Giemsa stained sections by demonstrating intervascular fibrin deposition in the reticular dermis. Immunoglobulin and complement deposition was not present. Thus the clinical induration of the LPR, like that of DH reactions, is apparently produced by trapping of tissue fluids in a fibrin gel generated by activation of the coagulation system in LPR. Possible mechanisms for this activation will be discussed later. Our unpublished studies of these reactions at 24 hours show marked perivascular lymphocytic infiltrates and fibrin deposition similar to DH

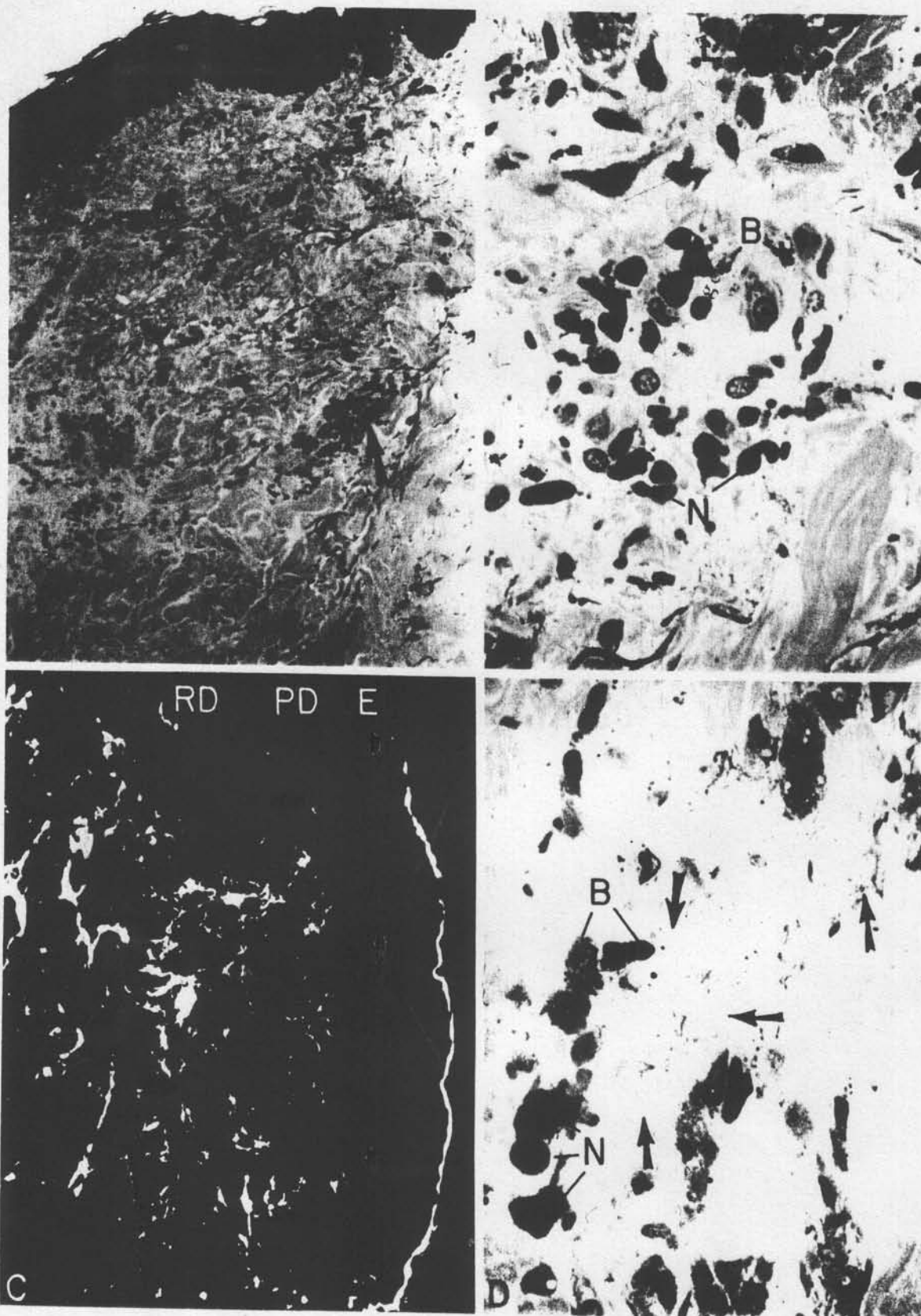
reactions. Richerson and colleagues noted similar cellular infiltration.²⁹ In agreement with our studies of six hour LPR no differences in histopathology were noted by these authors between isolated WFR and LPR at 24 hours.

Animal Models of LPR

Injection of rat skin with anti-IgE antibody, Compound 48-80, or isolated mast cell granules produces an area of mild, persistent, dermal edema, but no induration like that noted with human LPR.³¹ Biopsy of these reactions over time shows two phases: an early infiltrate of polymorphonuclear cells (PMN) appearing in 1-2 hours and peaking at 4-8 hours, and a mononuclear cell infiltrate replacing the PMN by 24-48 hours. These reactions had fewer eosinophils than human LPR,³² and fibrin is not present. Solubilization of the mast cell granule matrix with subsequent purification has demonstrated two active fractions capable of inducing these reactions.³³ The lower molecular weight factor has been purified and termed "inflammatory factor of anaphylaxis (IF-A)." Injection of this factor into rat skin produces biphasic histologic reactions without associated mast cell degranulation, and thus appears to be a key element in the generation of this reaction.

Interestingly, the histologic intensity of rat LPR-like reactions is somewhat inhibited by diphenhydramine, but greatly inhibited by diphenhydramine in combination with cimetadine. This inhibition does not occur if rat LPR-like reactions were induced by histamine-free mast cell granules.³⁴ How histamine could influence some but not all of these reactions is unclear, but may be related to histamine effects at vascular beds.³⁴ Rat LPR-like reactions are inhibited by corticosteroids.³⁵ Again, effects are different depending on how the reactions are induced. Those induced by anti-IgE and mast cell granules are more easily inhibited than those produced by low-molecular weight mast cell fractions.

Figure 1. Six hour late phase reactions induced with ragweed and studied in 1 μ m-thick, Epon-embedded, Giemsa-stained sections (A,B,D) or by immunofluorescence (C). A: low power overview indicating slight, largely perivascular inflammatory cell infiltrate (arrows) about vessels of the reticular dermis. B: higher magnification view illustrating the mixed cellular infiltrate characteristic of these reactions. L, lymphocytes; B, basophil; N, neutrophil. C: fresh frozen cryostat section stained with anti-human fibrinogen/fibrin. Note extensive fibrin deposits scattered in intervascular zones of the reticular dermis (RD) with relative sparing of papillary dermis (PD). Epidermis (E) is unstained except for artifactual linear staining of superficial stratum corneum. D: intervascular reticular dermis illustrating meshwork of fibrin strands (arrows) as well as basophils (B) and neutrophils (N). A, $\times$ 175; B and D, $\times$ 800; C, $\times$ 235. (Reproduced from (19) with permission of the publisher).



Although complement depletion has little effect on rat LPR-like reactions, neutrophil depletion appears to attenuate them.³⁶ These data on rat LPR-like reactions have been recently reviewed.³⁷

Possible Mechanisms of the LPR

From the previous paragraphs it seems likely that the mediator or mediators responsible for the human LPR are present in human dermal mast cells. Furthermore, although the role of histamine is still uncertain, it cannot be the sole or even the primary mediator of the reaction. Hypotheses as to the pathogenesis of the LPR must explain activation of the coagulation system with the resulting fibrin deposition so prominent in LPR. Furthermore, the sensation of burning, itching and pain to touch which is a consistent feature of these reactions must be taken into account. It is possible that multiple members of the intricate array of preformed, generated, and granule matrix derived mast cell mediators may be involved in these reactions, but a mediator with kallikrein-like activity seems to be an especially good candidate to play a central role. In this regard, a mast cell derived preformed mediator with kallikrein-like activity (BK-A) has been described, although it has not been demonstrated to activate Hageman Factor as does plasma kallikrein.^{38,39} Certainly the formation of bradykinin by this mediator could explain the burning and pain of LPR, but the role of bradykinin itself is probably limited. Bradykinin has been reported to be incapable of inducing biphasic dermal reactions in rats.³¹ Recently the injection of tissue kallikrein into human skin has resulted in the production of late phase reactions which are clinically and histopathologically identical to LPR induced by Compound 48-80.³⁹ These reactions were blocked by prednisone and demonstrated a refractory period like that of the antigen induced LPR. Further studies of kallikrein compounds may provide many missing pieces to the puzzle surrounding the pathogenesis of the LPR.

It has also been suggested that LPR may be the result of an intricate interplay between mast cells, basophils and eosinophils which has evolved for host defense against parasites.⁴⁰ Further investigation in this area should also be informative.

Associations between LPR and Allergic Diseases

Gleich has recently provided an extensive discussion of the possible relationships between the LPR and allergic diseases.⁴⁰ Suffice it to say the LPRs are of potential clinical importance as they relate to local reactions to allergen immunotherapy, insulin,¹⁷ insect stings,⁴¹ and probably local reactions to some immunizing agents. The possibility that some forms of atopic dermatitis may be a manifestation of mast cell derived mediator release has long been of interest, and has been recently readdressed.⁴² Some forms of chronic urticaria may be related to late phase reactions in the skin, although histopathologic studies to date have not pro-

vided support for such a hypothesis. More likely related to LPR are certain types of physical urticaria, such as steroid-responsive delayed pressure urticaria. Investigation is needed in this area, especially since combinations of H1 and H2 antagonists appear to be especially useful in some patients with chronic urticaria.⁴³

Late nasal obstruction of 6-12 hours after allergen insufflation has been reported to occur in 3-47% of nasal allergen challenges in patients with allergic rhinitis.⁴⁴⁻⁴⁶ These reactions were uncommon, however, both at six or 24 hours in a study by Richerson and colleagues, and there was no correlation between dermal LPR and late nasal reactions when they did occur.²⁹ H1 and H2 histamine antagonists in combination have been reported to be more effective than H1 antihistamines in blocking histamine-induced nasal reactions, but have not been evaluated in the treatment of late nasal obstruction.⁴⁷ Lemanske and Kaliner³⁷ have suggested that LPR in the nose may be responsible for a decreased threshold for induction of symptoms of allergic rhinitis similar to that produced in the lung after allergen induced late asthmatic reactions.⁴⁸

The possibility that the LPR is a paradigm for late bronchial reactions after allergen inhalation is an attractive, although unproven, hypothesis. Certainly recent data correlating circulating levels of neutrophil chemotactic activity (NCA), probably of mast cell origin, with immediate and late asthmatic reactions after allergen inhalation add support to such a concept.⁴⁹ Pharmacologic studies showing inhibition of both immediate and late bronchial reactions by cromolyn sodium and inhibition of the late asthmatic reaction by corticosteroids are also supportive.⁵⁰ There are many unexplained questions, however. Allergen inhalation can cause immediate, late, dual, persistent, or nightly asthma,^{50,51} a multiplicity of patterns not noted with dermal reactions to allergen. Perhaps this difference in the airways response can be explained by late bronchial reaction-induced exaggeration of normal diurnal variations in airway caliber. Several promising animal models of late bronchial reactions may help unravel the mystery of these responses.⁵²

Conclusion

The significance of the LPR, outside of the local reactions mentioned above, remains to be clarified. Studies of this response to date have pointed out that the classical concept of "immediate hypersensitivity" as a short-lived response to allergen is obsolete. Mast cell derived reactions may cause permanent symptomatology, and we are only just beginning to understand how.

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INGRATITUDE

"Nothing is in its nature so fleeting, nothing has a shorter existence than the remembrance of kind acts; and the greater they are so much the more likely are they, as the proverb says, to be paid by ingratitude; for he who cannot or will not cancel them by a return of kindness, often seeks to cancel them by forgetting their existence, or by making himself believe that they are after all not so very great; and those who are ashamed of having stood in need of a kindness are indignant at having received it, so that they have a stronger feeling of hatred from the recollection of the necessity into which they have fallen, than of obligation for the kindness which they have received."

Francesco Guicciardini
The History of Italy