

Systemic effects of local allergic disease

Alkis Togias, MD *Baltimore, Md*

Allergic reactions are not confined to the area they originated, but assume a secondary systemic, nonanaphylactic element. This element has two consequences: it feeds back into the site of the original reaction and it leads to the development of distant local manifestations. The well-established interactions between the nasal and the lower airways in allergic disease could be viewed as an example of this model. Interactions between the nasal mucosa and the paranasal sinuses, as well as interactions between the respiratory system, the skin, and the gastrointestinal tract have been described and may also fall under the same category. Two conduits of the systemic element of allergic disease are proposed: the systemic circulation and the nervous system. The mechanisms that lead to the development of the systemic element, and particularly the mechanisms of distant manifestations after a local allergic reaction have not been elucidated, but they probably include intricate interactions between the classic mediators of the acute allergic reaction, locally- and systemically-produced cytokines and neurotrophins, the vascular epithelium and the adhesion molecule system, the chemokine network, antigen-presenting dendritic cells and their interactions with T-lymphocytes, as well as a strong bone marrow component. From this perspective, the systemic element presents an exciting area of current and future research in allergic disease. (*J Allergy Clin Immunol* 2004;113:S8-14.)

Key words: Allergen challenge, basophils, mast cells, dendritic cells, adhesion molecules, neurogenic inflammation

For the prevention of development of allergic disease, an understanding of prenatal influences, as well as of the early influences of the environment are of utmost importance. For the management of ongoing allergic disease, however, we need to focus on the mechanisms of the allergic reaction and its short- and long-term consequences. During the past few years, many researchers have focused their attention on the systemic aspects of allergy. That allergic disease constitutes a systemic condition is a fact based on the mere presence of immunoglobulin (Ig)E antibodies in plasma and on the common knowledge that cells bearing specific IgE anti-

Abbreviations used

APC: Antigen-presenting cell
CFU: Colony-forming unit
Eo/B: Eosinophil/basophil
Ig: Immunoglobulin
IL: Interleukin
RSV: Respiratory syncytial virus
TNF- α : Tumor necrosis factor- α

bodies against an allergen that penetrates the body through a particular route (eg, the gastrointestinal tract) can be found in distant tissues (eg, the skin). The systemic aspects of allergy have recently attracted more attention because of a series of important observations indicating that local allergic reactions lead to manifestations at distant sites.

Our belief is that the systemic inflammatory events that are produced as a consequence of an allergic reaction at a specific local site have two functions: first, they feed back to the site of the original reaction and potentiate its local effects. For example, it is quite possible that late-phase reactions are manifestations of these systemic inflammatory events. Second, systemic inflammatory events lead to pathologic responses in other parts of the body. We, therefore, believe that the systemic aspects of allergy play a central role in the clinical manifestation of allergic diseases because they are responsible for the perpetuation and expansion of the pathologic process. Full appreciation of these reactions promotes the view of allergic diseases as whole-body syndromes, as opposed to constellations of localized allergic reactions. The implication of this view of allergy is that successful management requires integrated approaches targeting both the local and the systemic pathways. For the development of such approaches, we need to focus our research efforts in the elucidation of the mechanisms involved in the systemic manifestations of allergic disease and of the interplay between the local and systemic aspects.

A POSSIBLE PARADIGM OF THE SYSTEMIC ASPECT OF ALLERGY: THE RHINITIS-ASTHMA LINK

In 1992, Corren et al conducted an important study.¹ Ten patients with seasonal allergic rhinitis and asthma were challenged with nasal administration of allergen. Bronchial responsiveness to methacholine increased significantly 30 minutes after administration of the nasal challenge. This effect lasted for at least 4 hours. Radionuclide studies found no evidence of allergen deposition into the lungs; it was concluded that an allergic reaction taking place in the nasal mucosa had resulted in a distant

From the Divisions of Allergy and Clinical Immunology, and Pulmonary and Critical Care Medicine, Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland.

A. Togias is on the Speakers' Bureau for Merck, Pfizer, AstraZeneca, Genentech, and Novartis; he is on the advisory board for Baxter, Merck, and Aventis, serves as a consultant to AstraZeneca, Genentech, Novartis, and Schering-Plough, received study contracts from Alcon and Schering-Plough, and received study support from GlaxoSmithKline.

Reprint requests: Alkis Togias, MD, Divisions of Allergy and Clinical Immunology, and Pulmonary and Critical Care Medicine, Room 3B65B, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224.

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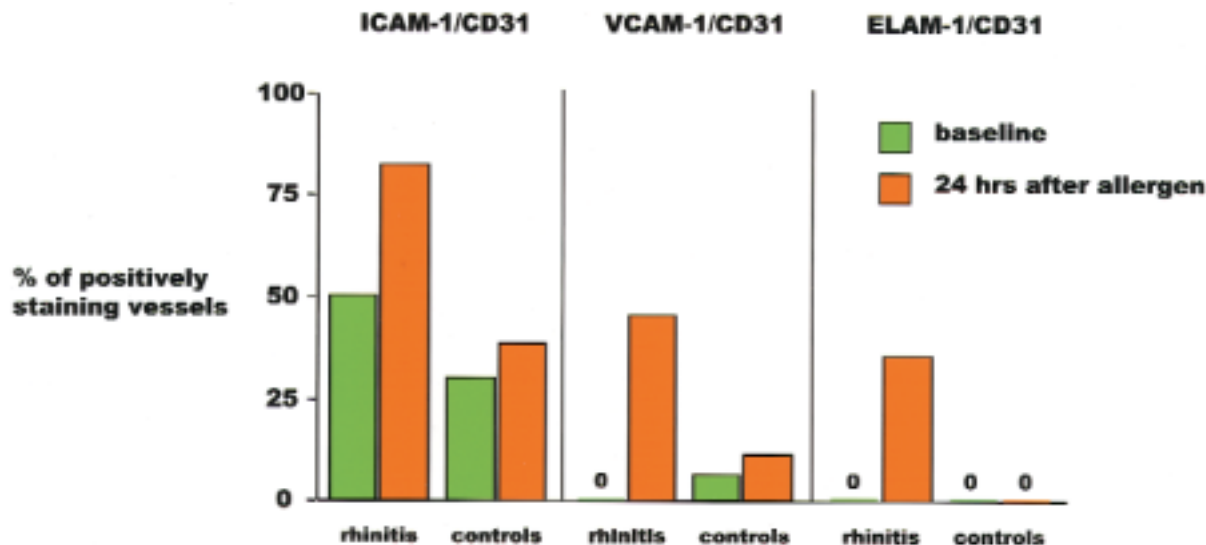


FIG 1. Expression of endothelial adhesion molecules (VCAM-1, ICAM-1, and E-selectin) on bronchial mucosal blood vessels after nasal allergen challenge. Levels were significantly increased in patients with allergic rhinitis compared with baseline values and with values seen in control subjects. CD-31 is a marker for endothelial cells. Adapted from Braunstahl GJ et al. *J Allergy Clin Immunol* 2001;107:469-76.

effect. In the next few years, our group produced similar results. We also found that, whereas lung function does not change immediately after nasal challenge, a significant reduction in forced expiratory volume at one second (FEV₁) and forced vital capacity (FVC) can be noted 6 hours later.^{2,3} Interestingly, this reduction was blocked by pretreatment with an oral antihistamine.³

The inverse concept has also been supported by experimental evidence. Several small clinical studies have suggested that administration of intranasal corticosteroids may improve asthma outcomes.⁴⁻⁹ For example, Welsh et al compared the use of several therapies in subjects with seasonal ragweed hay fever, including intranasal flunisolide, beclomethasone dipropionate, cromolyn, and placebo.⁶ In addition to nasal symptoms, they evaluated chest symptoms in a subgroup characterized by concomitant seasonal asthma. They found that the subjects in the asthma subgroup who received intranasal corticosteroids had almost complete elimination of seasonal (presumably pollen-induced) asthma symptoms. Findings supportive of an effect of rhinitis treatment on asthma were also reported in the retrospective analysis of the MarketScan database performed by Crystal-Peters et al.¹⁰ Yet, not all studies around this concept have shown positive benefits of allergic rhinitis treatment on asthma symptoms.^{11,12}

The above information implies an interaction between the upper and the lower airways in the context of the chronic allergic respiratory syndrome, but offers no clues as to its mechanism(s), other than the possibility that allergic inflammation in the nasal mucosa plays a pivotal role. Nevertheless, several mechanisms have been proposed, including the disturbance of the beneficial homeostatic and protective role that the nasal mucosa plays for the entire respiratory tract the possibility of a neural inter-

action between the upper and lower airways (part of which may be mediated by the so-called nasobronchial reflex), and the irritating/inflammatory effects of secretions from the nasal airways and the paranasal sinuses finding their way into the lower airways.¹³ One more proposed mechanism is the systemic propagation of inflammation from the nasal to the lower airway mucosa.^{14,15}

In a recent seminal study, Braunstahl et al investigated mucosal inflammation and adhesion molecule expression in both the upper and lower airways after nasal allergen provocation.¹⁶ Nine subjects with seasonal allergic rhinitis and 9 healthy control subjects underwent a nasal provocation with grass pollen extract. Nasal and bronchial biopsies were performed at baseline and 24 hours after provocation. After 24 hours, both nasal and bronchial eosinophils were significantly increased compared with baseline values and with the control subjects. Also at 24 hours after nasal allergen challenge, a statistically significant increase in the expression of the adhesion molecules ICAM-1, VCAM-1, and E-selectin on the bronchial endothelium was observed in patients with allergic rhinitis compared with baseline values and with the control subjects (Fig 1). This study offered good evidence that a localized allergic reaction can induce inflammatory changes at a distant site and can be regarded as the first solid experimental evidence for the concept of systemic propagation of the allergic reaction. Braunstahl et al have also found in subjects with allergic rhinitis that a bronchial provocation with allergen delivered into a subsegmental bronchus through the wedged bronchoscope technique led to increased inflammatory markers in the nasal mucosa.^{17,18} This bidirectional systemic cross-talk between the upper and lower airways offers further evidence of systemic propagation of allergic inflammation.¹⁹

FURTHER SUPPORT FOR THE SYSTEMIC PROPAGATION OF LOCALIZED ALLERGIC REACTIONS

Several studies indicate that the phenomenon of systemic propagation of allergic reactions occurs over the entire spectrum of allergic diseases. In the airways, another striking example has been offered by Baroody et al, who have developed a model of nose–sinuses interaction.²⁰ This model involves the insertion of a catheter into one or two maxillary sinuses allowing for repetitive sinus lavages and for evaluation of humoral and cellular inflammatory elements in sinus fluids. These investigators have recently reported in abstract form that unilateral (in a single nostril) nasal provocation with allergen results in late elevations of albumin and in increased number of eosinophils in the ipsilateral and contralateral maxillary sinuses.²¹ One could argue that, perhaps, allergen sprayed in one nostril may reach the ipsilateral maxillary sinus, although even this seems unlikely. It is difficult, however, to offer any explanation for the contralateral sinus findings other than that they represent a distal manifestation of the originally localized nasal allergic reaction.

There has been plenty of speculation on the relationship between atopic dermatitis and sensitization to aeroallergens and food allergens.^{22–24} Although it is reasonable to assume that aeroallergens may induce cutaneous manifestations through direct contact with the skin of sensitized persons, the possibility that the skin problem may reflect systemic propagation of an allergic reaction originally occurring in the respiratory mucosa needs to be entertained. In 1997, Brinkman et al showed that dust-mite allergen inhalation challenge can cause a flare up of skin lesions in patients with pre-existing atopic dermatitis and dust-mite sensitization.²⁵ The worsening in the clinical score for dermatitis occurred around 24 hours after the inhalation challenge and no acute cutaneous symptoms were noted. Interestingly, the effect of the inhalation challenge on the skin was more pronounced in the subjects who also had asthma, as opposed to those who only had allergic rhinitis. Another group has reported similar findings.²⁶ Food allergy has long been associated with atopic dermatitis.²⁷ Sampson et al have conducted several important studies evaluating the effect of oral provocation on skin lesions, primarily in children with atopic dermatitis and food hypersensitivity documented through skin testing. In the majority of these children, ingestion of such a food led to manifestations in the skin²⁸; in some subjects, the respiratory tract was affected as well.²⁹ The time course of these reactions varies from less than 1 hour to as many as 24 hours. Also, the quality of the cutaneous lesions is variable, indicating that, perhaps, depending on time and lesion, the mechanisms differ. For the cutaneous and respiratory manifestations appearing hours after ingestion of the provocative food, the hypothesis of systemic propagation of the allergic reaction from the gastrointestinal mucosa to the skin or the respiratory mucosa offers a reasonable possibility.

HOW DOES A LOCAL ALLERGIC REACTION PROPAGATE SYSTEMICALLY?

It is possible that allergen is slowly absorbed from the site of its original contact with the body (the respiratory or the gastrointestinal mucosa) into the peripheral blood and that it is picked up by mast cells and antigen presenting cells in various organs. This would lead to the observed distant-local reactions. This hypothesis has at least two theoretical problems. First, one would expect that systemically absorbed allergen would initially activate basophils in the peripheral blood before reaching distant tissues and that basophil activation would lead to generalized reactions resembling anaphylaxis. Such reactions are conspicuously absent after allergen provocation, at least in the respiratory tract. The second problem is that systemically absorbed allergen would be uptaken by every mast cell in every tissue, on the basis of the assumption that every one of these cells carries specific IgE recognizing allergens against which allergic sensitization has occurred. If so, an allergic reaction induced in the nasal mucosa should simultaneously result in manifestations from the bronchi, the skin, the heart, the gastrointestinal tract, etc. Yet, it has never been reported that allergen inhalation challenge causes cutaneous changes in subjects who do not have atopic skin disease.

A variety of other mechanisms can be proposed, through which a local allergic reaction could lead to late distant manifestations (Fig 2). Yet, no evidence exists supporting one such mechanism over the other. In fact, it is quite possible that the above-described phenomena reflect a constellation of various interactive or even independent pathways.

An acute allergic reaction that takes place at an original tissue site results in the release of mast cell products that have two major functions: first, they affect various tissue elements (vascular and nonvascular smooth muscle, glands, nerves, endothelium) to induce the classic acute allergic symptoms; second, they activate other cells to release cytokines and chemokines, and to express adhesion molecules. Some of the mast cell products possess both functions. For example, histamine, in addition to its effects on the vasculature and on sensory nerves, may impact surrounding lymphocytes.^{30,31} Sulfidopeptide leukotrienes can play a chemo-attractive role for eosinophils³² and may prolong their survival.³³ Eosinophils carry the cysLT1 receptor.³⁴ Although the effect of sulfidopeptide leukotrienes on other immune cells has not been elucidated, the cysLT1 receptor has been identified on several additional immune cells, including macrophages/monocytes³⁴ mast cells³⁵ and even T-lymphocytes.³⁶ Mast cells also produce tumor necrosis factor (TNF)- α , which has primarily cytokine functions³⁷; additional cytokines such as interleukin (IL)-4 and IL-5 may be produced by these cells, although this is under debate.

Based on the plethora of mast cell products and the multiplicity of their actions, one could hypothesize that the systemic effects of an allergic reaction may be secondary to mast cell activation. For example, it is possible

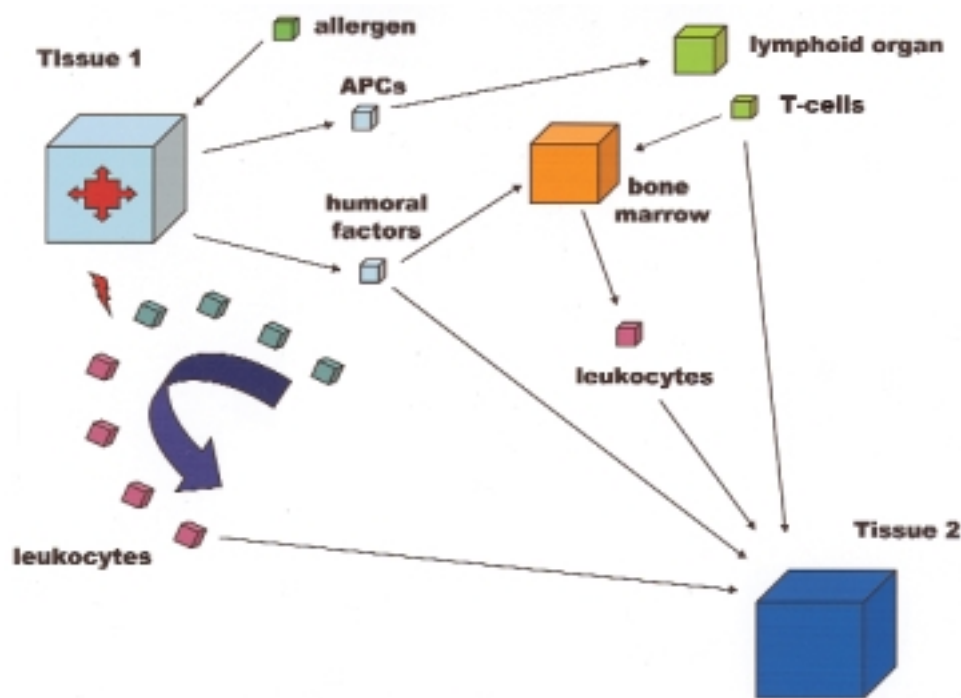


FIG 2. Diagrammatic presentation of possible pathways involved in the development of distant inflammation (in Tissue 2) after a localized allergic reaction (in Tissue 1). As a result of the allergic reaction in Tissue 1, increased expression of adhesion molecules at the postcapillary venules can lead to activation of circulating leukocytes which, in turn, may home in distant tissues (Tissue 2). In addition, humoral factors deriving from the original reaction circulate in the blood and may affect Tissue 2. Antigen-presenting cells transport allergens to lymphoid organs and present them to T-lymphocytes. T cells are, thus, activated and enter the circulation. These cells will home at the original allergic reaction site, but could also home in the bone marrow or in other tissues (Tissue 2). Bone marrow leukocyte precursor cells can also become activated and begin to circulate, either because of cytokines from newly arrived lymphocytes or because of circulating humors.

that some of the inflammatory mediators and cytokines produced by the original allergic reaction circulate in the peripheral blood (it is known that histamine levels increase in the blood and sulfidopeptide leukotriene levels increase in the urine after experimentally-induced allergic reactions in humans)^{38,39} and activate peripheral leukocytes or even leukocytes that are resident in distant tissues. Another possibility is that circulating leukocytes become activated when passing through the postcapillary venules of the tissue in which the original allergic reaction took place. The endothelium of these venules may newly express adhesion molecules as a result of the release of cytokines (eg, $\text{TNF-}\alpha$) from mast cells. Although the role of adhesion molecules is to allow for cells to attach to the endothelium and eventually transmigrate, many leukocytes may only become momentarily attached; however, this brief encounter with adhesion molecules is capable of initiating activation signals.

There is good evidence that a local allergic reaction can lead to peripheral blood cell activation. For example, we recently reported in abstract form that repetitive administration of allergen in the nose of human subjects with allergic rhinitis leads to increased ex vivo spontaneous release of IL-13 from basophil-enriched peripheral blood cells, to increased expression of the β chain of the high

affinity IgE receptor on basophils and to increased spontaneous production of mRNA for $\text{TNF-}\alpha$ from basophil-depleted peripheral blood cells.^{40,41} Lönnkvist et al recently showed that the ability of peripheral blood eosinophils to transmigrate spontaneously, ex vivo, was significantly increased in children 2 hours after nasal allergen provocation.⁴² In naturally occurring allergic disease, many studies have directly or indirectly documented the state of activation of various leukocytes including basophils, eosinophils, lymphocytes, and monocytes.

Another major pathway that can be proposed in explaining the systemic propagation of a local allergic reaction is the dendritic cell-T lymphocyte axis. Dendritic cells are the main antigen-presenting cells (APCs), at least in the respiratory mucosa. After engulfing allergenic particles, these cells become activated and migrate to adjacent lymphoid organs where they present allergen-derived peptides to T-lymphocytes leading to their respective activation.⁴³ T cells will either further activate B lymphocytes in the lymphoid organ or will enter the circulation and will migrate to the tissue where the original allergic reaction took place. There, they will participate in the local development of inflammation utilizing the panoply of strategic molecules they are capable of producing.⁴⁴ The possibility exists, however, that activat-

ed T-lymphocytes may also enter tissues other than those where the original allergic reaction took place and may promote inflammation in those tissues as well.

In the process of systemic propagation of allergic inflammation, one should not omit the potentially central role of the bone marrow. In a series of important studies, Denburg and colleagues have provided evidence on various aspects of bone marrow activation in humans and animals, in the course of the natural history of allergic disease, as well as after experimental allergen exposure. For example, higher numbers of eosinophil/basophil (Eo/B) colony-forming units (CFUs) and CD34⁺ hematopoietic progenitors have been found in the blood of atopic compared with healthy persons and the number of these cells has been shown to fluctuate in accordance with seasonal allergen exposure.⁴⁵⁻⁴⁷ Also, allergen inhalation challenge has been shown to lead to increased Eo/B CFUs and hematopoietic progenitors in peripheral blood.⁴⁸ Recently, Wood et al examined the effect of allergen challenge on the bone marrow in human subjects.⁴⁹ Subjects with allergen-induced isolated early reactions and subjects with both early and late asthmatic response (dual-responders) were given an allergen inhalation challenge. At 24 hours after the challenge, there were significant increases in the percentages of bone marrow CD3⁺ cells (T-lymphocytes), IL-5 mRNA⁺, and IL-5 mRNA⁺/CD3⁺ cells in both groups. However, dual responders showed significantly higher increases compared with the early responders. These observations were combined with higher eosinophilia in the airway mucosa of the dual responders. These results suggest that, after a local allergic reaction, T-lymphocytes are attracted to the bone marrow, release cytokines, and cause the proliferation/maturation of eosinophils and basophils. In persons who develop late allergic responses, this cascade appears to be exaggerated. This process represents one aspect of the model that places the systemic elements of the allergic reaction in a central position, when the mechanisms of perpetuation and propagation of allergic inflammation are to be considered.

As mentioned above, systemic pro-inflammatory effects on leukocytes may not only derive from cytokines, but from some of the classic acute products of the allergic reaction. This may be the case in peripheral blood, but also in the bone marrow. Braccioni et al evaluated the effects of leukotrienes (LTD₄ and LTE₄) and the cysLT₁ receptor antagonist montelukast on peripheral blood and bone marrow eosinophil-basophil progenitor growth in atopic subjects.⁵⁰ Peripheral blood Eo/B CFUs grown in the presence of granulocyte-macrophage colony-stimulating factor and bone marrow Eo/B CFUs grown in the presence of IL-5 were significantly increased by the addition of LTD₄ (0.1 μ mol). This increase was suppressed by montelukast (1 μ mol) indicating that it is a cysLT₁ receptor-mediated effect.

Many of the pathways I have described involve the migration of cells into tissue sites that are different from those where the original allergic reaction took place. Why does this happen? It is generally accepted that

leukocyte trafficking is highly dependent on the pattern of adhesion molecules expressed by endothelial cells. In addition, some leukocytes exhibit specific tissue homing characteristics that also depend on the pattern of adhesion molecules that are expressed on their surface. For lymphocytes, specific patterns of adhesion molecule expression may determine their homing behavior in the skin⁵¹ or the bronchial tissue.⁵² One should, therefore, expect that the development of inflammation distal to the site of an original allergic reaction first involves upregulation of adhesion molecules. This is exemplified by the work of Braunstahl et al described earlier in this article, where influx of eosinophils in the bronchial mucosa, after a nasal allergen provocation, was accompanied by significant increases in the expression of adhesion molecules (Fig 1).¹⁶ What is not known, however, is what determines the site of upregulation of the cellular attraction system. For example, is pre-existing, low level inflammation at the distal site a prerequisite or is the pattern of development of distant inflammation dependent on some background characteristics linked to the clinical phenotype? These and many other questions constitute an important new area of research in allergic disease.

THE NERVOUS SYSTEM: ANOTHER IMPORTANT SYSTEMIC CONDUIT FOR THE PROPAGATION OF THE ALLERGIC REACTION

The systemic circulation is only one of two major pathways through which allergic reactions propagate from one part of the body to the other. The nervous system is certainly the other. Central reflexes allow for communication between various body parts and particularly between parts of the respiratory tract. The output of these reflexes can increase as a result of an inflammatory process at various sites along its path. Additional "connections" may become functional via the effects of allergic inflammation. Inflammation-induced plasticity, therefore, is the characteristic of the nervous system that allows for the development of various tissue-to-tissue communications beyond its physiologic function.

An example of upregulation of the nervous system in relation to allergic inflammation is the nasosnasal reflex. Stimulation of the nasal mucosa in one nostril with a stimulus that affects sensory nerve endings (histamine, bradykinin, capsaicin, hyperosmolar saline) results in an ipsilateral secretory response. In a few healthy persons, a contralateral response can also be detected; various studies have confirmed that the contralateral response is neurally mediated.^{53,54} However, the overall contralateral response in healthy subjects or in persons with seasonal allergic rhinitis tested out-of-season is minimal and for many stimuli not statistically significant.^{54,55} In contrast, in subjects with perennial allergic rhinitis, or in those with symptomatic seasonal disease, the nasosnasal secretory reflex becomes highly evident.^{54,55} With capsaicin, the difference between healthy subjects and subjects with perennial allergic rhinitis in both the ipsilateral and the contralateral secretory responses is more than 100-fold.⁵⁶ Another

example of a reflex that integrates 2 parts of the respiratory system is the so-called nasobronchial reflex.¹³ The existence of such a reflex, which manifests itself with bronchial obstruction after nasal stimulation, has been under debate with some authors supporting its existence⁵⁷⁻⁵⁹ and others questioning it.⁶⁰ Perhaps the controversy exists because this reflex may only be evident in persons with persistent strong inflammation of the nasal mucosa; this issue has not been thoroughly examined.

Along the path of a central reflex, several targets can be identified and several mechanisms have been proposed to explain the upregulation of the system in the context of allergic inflammation.⁶¹ Increased responsiveness at the sensory nerve ending of the loop may result from decreased action potential threshold or increased number of sensory nerve endings (nerve sprouting). Some cytokines and neurotrophins are capable of inducing such changes. Nerve growth factor, for example, is produced locally in the course of an allergic reaction and may play a significant role in this process.⁶² Other sites that can be affected as a result of allergic inflammation include the sensory ganglia,⁶³ the central neural junctions of sensory neurons at the level of the brain stem, and the preganglionic and postganglionic junctions of the efferent neurons of the reflex.⁶⁴

CONCLUSIONS

Although the initial manifestations of a mucosal allergic reaction are localized, a systemic component develops as well. This component may play two roles: (1) it can feed back into and perpetuate the original local reaction, and (2) it can lead to the development of distant local reactions. The conduits of the systemic component are the systemic circulation and the nervous system, but the mechanisms that are involved in the development and manifestation of the systemic component are not understood. Yet, viewing allergic disease as a systemic illness, as opposed to independent local ailments, may offer new insights into its pathophysiology and may lead to new ideas regarding the optimization of treatment strategies.

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