strictor agonists. Together, these data suggest a role for the NANC inhibitory nervous system in preventing or attenuating bronchospasm.

The functional significance of the airway NANC inhibitory system remains to be defined. It has been suggested that a defect in the function of airway NANC inhibitory innervation may contribute to the elevated airway reactivity observed in asthmatic individuals. The observation that ganglionic blockade does not enhance the airway reactivity of normal subjects would argue against such a contention,\(^6\) since efferent autonomic nerve impulse traffic from the central nervous system to the airways would be blocked. However, bronchomotor responsiveness in normal subjects may be affected by nervous (eg, adrenergic and NANC) and non-nervous (eg, arachidonic acid metabolite) inhibitory influences. Non-nervous influences may be sufficient to regulate airway reactivity under conditions of autonomic blockade. As such, inhibition of both neural and non-neural influences may be necessary to induce a state of bronchial hyperreactivity in normal subjects. In addition, a local reflex may exist in the lung to regulate airway responsiveness, such that an axo-axonal connection would exist between afferent nerves and postganglionic NANC inhibitory nerves. This local reflex would allow the conduction of action potentials from afferent nerves to efferent NANC nerves without the involvement of the central nervous system and peripheral autonomic ganglia. Precise determination of the role of the NANC inhibitory system in the regulation of bronchomotor tone under physiologic and pathophysiologic conditions requires the use of a specific NANC inhibitory receptor antagonist, which has yet to be developed.

Aside from effects on airway smooth muscle, the NANC inhibitory system may regulate other lung functions, such as mucus secretion, mediator release or pulmonary vascular tone, and epithelial or endothelial permeability. Exploration of these other possible regulatory roles of the NANC system may provide valuable insights into the normal and abnormal physiology of the lung.

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Neurohumoral Regulation of Airway Contractile Responses

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Bronchomotor tone is the net product of moment-to-moment interactions between the autonomic nervous system, circulating humoral influences, and endogenous production of locally secreted mediators.

Some degree of airway smooth muscle contraction exists in all individuals. In normal persons, it appears to result largely from parasympathetic innervation to the airway.\(^1\) Endogenous bronchomotor tone theoretically is antagonized physiologically by inhibitory parasympathetic reflexes and by circulating epinephrine.\(^4\) Direct innervation to human airways by sympathetic nerves is insignificant. The homeostatic role of sympathetic secretion in regulating broncho-

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motor tone, however, remains to be defined. Recent investigations indicate that endogenous secretion of catecholamine does not increase during bronchocstriction, unless it is associated with severe hypoxemia or hypotension.

Nonadrenergic inhibitory innervation (NAI) is capable of antagonizing exogenously induced changes in bronchomotor tone. However, the NAI system also is not activated by changes in airway caliber, and the homeostatic significance of this system for airway innervation also remains undefined.

In asthmatic individuals, bronchomotor tone is increased substantially. Because parasympatholytic agents largely are ineffective in treating asthma, it appears that this increase is not related substantially to increased parasympathetic activity. Scores of other contractile influences have been suggested to account for the increase in bronchomotor tone in asthmatic individuals. The role of beta-adrenergic "deficiency" seems questionable, since normal individuals show no increase in airway reactivity even under conditions of nearly complete beta-adrenoceptor blockade.

Recent studies have elucidated mechanisms for modulation of bronchomotor tone by the overlying airway epithelium and the underlying serosa from which neurohumoral and fixed and circulating blood elements are transported. The epithelium appears to secrete mediator(s) that cause tonic inhibition of bronchomotor tone. Removal of the epithelial layer augments airway contractile responses in dogs to acetylcholine, histamine, and serotonin in vitro. However, these experiments have been performed under conditions greatly removed from the physiologic state, and there is a need to establish the inhibitory role of bronchial epithelium in situ.

Under other circumstances, products of granulocytic infiltration and, perhaps, environmental insults (eg, ozone) elicit airway hyperreactivity that appears to be regulated at least in part by the bronchial epithelium. Neutrophilic infiltration appears to be an essential component of immune-mediated airway hyperreactivity in the rabbit. The major basic protein of eosinophils appears to augment airway contractility of airway smooth muscle when applied to the tracheal epithelium of the guinea pig.

Regional secretion of mediator long has been thought to underlie the pathogenesis of asthmatic bronchoconstriction. However, no specific pharmacologic antagonist reverses asthmatic bronchoconstriction, and all effective therapeutic agents currently used elicit bronchoconstriction by stimulating inhibitory receptors on airway smooth muscle. This finding may reflect the virtual certainty that during asthmatic bronchoconstriction—and perhaps chronically in asthmatic subjects—many mediators are secreted simultaneously. Antagonism of a single agent among the amine, peptide, and lipid mediators of airway contraction in this state would not be expected to elicit substantial inhibitory effects.

A major unsolved question is the mechanism by which morphologically normal airway smooth muscle is transformed in the asthmatic state to a hypercontractile tissue that also is more difficult to relax. Most investigations have focused on animal models of airway reactivity to agonists taken one at a time. However, several studies have shown that airway contractility to relatively weak agonists may be augmented substantially in the presence of a second agonist postsynaptically. Other studies have suggested that postsynaptic mediator-mediated interactions increase refractoriness to airway relaxing influences, such as isoproterenol. These data point to the need to consider models of airway hyperreactivity that results from complex postsynaptic interactions between regionally secreted mediators.

Similar consideration has been applied to bronchoconstriction elicited by mediators secreted from respiratory mast cells and circulating blood elements. Mast cell secretion is a dynamic process, which itself is regulated by endogenous secretory influences. Beta-adrenergic stimulation may substantially downregulate mast cell secretion of preformed mediators such as histamine and de novo synthesis of bronchoactive products of the lipoxigenase and cyclooxygenase pathways. Parasympathetic influences may augment mast cell secretion of mediator to antigenic stimulation.

Considerable recent attention has focused on the role of platelet activating factor (PAF), a lipid secreted from numerous cells, including mast cells, during immune activation. The complex interactions of this mediator in eliciting bronchoconstriction typifies the multieffect action of some mediators in eliciting bronchoconstriction. In the dog, PAF causes hypotension comparable to that in anaphylaxis. This appears to result from a direct effect of PAF on vascular smooth muscle. PAF also is an extremely potent contractile agent in canine airways; however, this does not appear to result from any direct action of PAF on an airway smooth muscle receptor. PAF causes release of serotonin from platelets, and its actions in causing airway smooth muscle contraction in vitro are blocked completely by serotonin or by pretreatment of platelets with receptor specific PAF antagonist. In vivo, contractility elicited by PAF is blocked partially, but not completely, by atropine but is unaffected by ganglion blockade with hexamethonium. This indicates a second mode of action, where contraction results from postganglionic stimulation of efferent parasympathetic nerves. A similarly complex mode of action has been suggested for substance P, which also acts at least in part through parasympathetic activation. Future investigations are likely to uncover even more complex actions of single mediators, further compounded, of course, by subsequent mediator-mediator interactions.

The complexity of these interactions is confounding, and research continues to be focused clarifying the relevant mechanisms that underlie airway hyperreactivity. The innovations of cellular and molecular biological investigations now in progress will serve to elucidate these mechanisms in the next generation.

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The Late Asthmatic Response*

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Late phase reactions have been observed in the skin¹ as well as the upper² and lower airways of man.³ The late phase reaction within the lower airways, the late asthmatic response (LAR), occurs hours after exposure to an appropriate stimulus and for many reasons is thought to resemble more closely the problems for which patients seek assistance than the immediate asthmatic response (IAR) that occurs within minutes of challenge. For example, the airway obstruction produced during LAR may be more severe and prolonged than that associated with IAR.³ In addition, the IAR may be easily reversed with inhaled or injected adrenergic drugs, while the LAR is less responsive to this form of therapy. While pretreatment with cromolyn prevents both IAR and LAR, corticosteroids given just before antigen exposure will not prevent IAR but will abolish or diminish LAR. The LAR has also been noted to correlate with frequent attacks of asthma and under laboratory conditions may occur in as many as 50 percent of challenged subjects.⁴ LARs that occur after either laboratory or natural exposure to antigen have been associated with subsequent increases in airways reactivity.⁵ This finding has led to the hypothesis that atopic asthmatic patients with LARs may develop a vicious circle in which heightened airway reactivity leads to enhanced responsiveness to allergens and nonimmunologic stimuli such as irritants and exercise,⁶ thus producing more persistent symptoms of asthma.

This review presents current thoughts on possible mechanisms that lead to the LAR. While the focus is on the antigen-induced LAR, observations of late phase reactions in the skin (late cutaneous response) and upper airways (late nasal response) that may give clues to the immunopathogenesis of late phase reactions in the lung are also cited.

**IMPORTANCE OF ANTIGEN-SPECIFIC IGE IN ANTIGEN-INDUCED LAR**

Studies by Pepys et al⁷ in patients with allergic bronchopulmonary aspergillosis and late reactions in skin and lung led to the hypothesis that late reactions were ARthus phenomena. However, recent studies of late phase reactions in the skin suggest that events with this time course are not necessarily type 3 events. For example, Solley and associates⁸ reported heating of atopic human serum used for passive sensitization reduced the capacity to transfer immediate and late cutaneous responses. Removal of IgE by passing the serum over an anti-IgE immunoadsorbent abolished the ability to transfer the reactions, while IgE from the immunoadsorbent restored the responses. Thus, within the skin of man, the evidence is strong that late responses to antigen can be dependent on IgE. The hypothesis that late phase reactions within the airways may also depend on IgE is more difficult to study in man. A recent report by Kirby et al⁹ did find that inhalation of sheep anti-human IgE led to LAR in one atopic asthmatic patient. With use of a rabbit model of the LAR, the importance of antigen-specific IgE and IgG to this pattern of airway obstruction has been investigated in more detail.⁰ In a study involving neonatal immunization to Alternaria tenuis, rabbits with predominantly or only IgE to this mold developed both early and late airway obstruction.¹ When rabbits were passively sensitized with intravenous infusions of sera containing IgE to this antigen, late responses were again noted. In both actively and passively sensitized rabbits, antigen-specific IgG appeared to blunt the LAR in immune rabbits. Evaluation of histologic specimens did not show evidence of immunoglobulin and complement deposition in the lungs of rabbits with late re-