Airflow-induced Bronchoconstriction in Humans

Arthur N. Freed, Ph.D.,* Carol A. Hirshman, M.D.C.M.†

BRONCHIAL ASTHMA is a variety of diseases characterized by reversible airflow obstruction and a heightened responsiveness of the airway to physical, chemical, and pharmacologic stimuli. This latter phenomenon is viewed as a key component of these diseases, and research has thus focused on understanding the mechanisms underlying this increased airway responsiveness associated with asthma.

It has been known for almost 19 centuries that physical exertion can provoke or worsen asthma,1 and for at least 122 years that breathing cold air can trigger an asthma attack.2 In the late 1970s, several investigators noted that asthmatic patients developed greater airway obstruction when breathing cold dry air during exercise than when breathing warm moist air, and concluded that either heat loss or water loss was the inciting stimulus.3,4,5,6,7,8,9 Since then, dry air-induced airway constriction has been intensively studied in the forms of cold air, exercise, and hyperventilation-induced airway obstruction. Although subtle differences in mechanism may exist, we refer collectively to airway responses resulting from these various forms of dry air perturbation as airflow-induced bronchoconstriction (AIB). Responses to these challenges have been investigated primarily in asthmatic individuals, but normal individuals respond in a similar, although attenuated fashion.2,4,5,6,7,8,9,10,11 The mechanism or mechanisms responsible for AIB are unknown, although interest has focused on the stimuli that trigger this form of non-specific airway responsiveness. Several hypotheses have been proposed,5,10,11 although none accounts for all the observations concerning AIB.

AIB occurs in approximately 75–80% of patients with asthma.8,9 Why this occurs in response to lesser stimuli, or with greater frequency in asthmatics than in normal individuals, remains unclear. Does this phenomenon complicate the anesthetic management of patients? It is unlikely that the maximal passive flow rates that occur during anesthesia reach the flow rates required to precipitate bronchoconstriction. On the other hand, fluid lining the airways of intubated animals exhibits elevated osmolarities,10,11 and it is conceivable that the resultant airway desiccation that accompanies prolonged administration of dry gases may provoke bronchoconstriction or potentiate irritant-induced bronchoconstriction in patients with asthma. An understanding of AIB is important to the anesthesiologist, not because anesthetics may conceivably provoke, potentiate, or attenuate AIB, but rather because AIB serves as a model of human asthma. An understanding of the mechanisms involved in AIB will provide insights into the mechanisms underlying airway reactivity in asthma. This will ultimately lead to better treatment and prevention of asthma, and decreased incidence of anesthetic complications in this high-risk patient population.

Exercise-induced asthma (EIA) and airway hyperreactivity are topics of great interest and, as such, are the subjects of a variety of recent reviews.3,4,5,6,7,8,9,10,11 The purpose of this work is to review the current literature focusing on responses to airflow drying in humans and in animal models,5,6,7,8,9 to contrast old and new hypotheses, and to evaluate these ideas in an attempt to further our understanding of human airway hyperreactivity and AIB.

Pathogenetic Mechanisms

It is possible that asthmatics represent a separate group uniquely different from the normal population.11 This implies that pathologic mechanisms underlying bronchial reactivity in normal and asthmatic subjects are qualitatively different. It is more likely that bronchial reactivity is distributed in the human57,155 and animal58,155 populations along a bell-shaped curve with asthmatic subjects
LUMEN

CONGESTED

CONTRACTED

SMOOTH MUSCLE

VAGAL EFFERENT

NC-NA EFFERENT

NC-NA EFFERENT

BLOOD

H2O/HEAT

FIG. 1. Diagram of hypothetical action and interaction among airway components believed to participate in the cascade of events that result in airflow-induced bronchospasm (AIB). CNS = central nervous system, EPI = epithelial cell, PMN = polymorphonuclear leukocyte, EOS = eosinophil, MAST = mast cell, LTB4 = leukotriene B4, LTs = other leukotrienes, PAF = platelet activating factor, TxA2 = thromboxane A2, PGs = prostaglandins, SP = substance P, Ach = acetylcholine, VIP = vasoactive intestinal polypeptide, NC-NA EFFERENT = noncholinergic-nonadrenergic efferent. Artistic license accounts for the platelet being located in the interstitium.

representing the most sensitive extreme of the population. This implies that the mechanisms underlying airway hyperreactivity in asthma are quantitatively, not qualitatively, different from those of the normal population. The underlying mechanisms are not known, but research has focused on: 1) abnormal autonomic control, 2) increased presence of inflammatory cells and mediators, 3) defects in epithelial function, and 4) abnormal airway smooth muscle function per se and/or increased sensitivity of smooth muscle to physical and chemical stimuli.

ABNORMAL AUTONOMIC ACTIVITY

The parasympathetic nervous system (fig. 1) has the potential to play a central role in bronchoconstriction in all mammals, and may function to modulate airway tone.118 Beta-adrenergic sympathetic nervous activity appears to counterbalance the effects of the parasympathetic system.76 In human airways, the major efferent innervation is via cholinergic nerves, which travel in the vagus and synapse in ganglia in the airway wall. These cholinergic nerves release acetylcholine, which stimulates muscarinic receptors. These receptors are blocked by cholinergic antagonists such as atropine, glycopyrrolate, and ipratropium bromide.

Cholinergic reflex activity may be exaggerated in asthmatics and lead to AIB. This has been indirectly demonstrated after cold air challenge using atropine pretreatment in asthmatic,67,127,140,154,155 nonasthmatic,75 and normal subjects with viral upper respiratory tract infection.8 Although baseline pulmonary function was not significantly affected in most of the studies cited, small alterations in baseline pulmonary function may in part account for the protection provided by this drug. In addition, cholinergic blockade appears ineffective in asthmatics, and in at least one animal model of AIB,50 when extreme thermal loads are involved.56,67

As a result of damage to the bronchial mucosa,77 the submucosal nerve endings of asthmatics may be more sensitive to airway cooling and drying. Initially, topical anesthesia of the airway with lidocaine was thought to inhibit EIA,43,103 although more recent studies find it relatively ineffective.51,68,129 This suggests that submucosal nerve endings are not hyper-excitabile, and AIB is not primarily mediated via "irritant-like"45,109 or thermally sensitive68 neuronal receptors. Cholinergic pathways apparently are involved in AIB in both asthmatic and normal humans, but in asthmatics, other mechanisms also contribute to AIB. Exaggerated cholinergic reflex activity, if present in asthmatics, may be the result of a primary defect, such as chronic mediator release, rather than the cause of abnormal physiological responses.

Airway responses to aerosolized distilled water or “fog”-induced bronchoconstriction appear to share pathways of action similar to those responsible for AIB.19,58 Exercise-induced bronchospasm more closely correlates with the level of nonspecific bronchial responsiveness as measured by distilled water challenge, than by methacholine aerosol challenge.53 Although data to the contrary exist,50,56,67,130 evidence from studies examining the effect
of atropine on dry air,57,82,83,127,141,154 and "fog"-induced bronchoconstriction55,59,116,128 suggest that a parasympathetic reflex pathway plays a role in at least some asthmatic subjects, and several animal models of asthma.

Three lines of evidence suggest that beta adrenergic bronchodilating mechanisms are important in protecting against bronchoconstriction in asthmatics. First, although beta adrenergic blocking drugs have no effect on airways of normal subjects, they cause bronchoconstriction in asthmatics.157 Second, beta adrenergic agonists, and especially beta2 selective agonists, are effective in preventing or attenuating AIB in human2,111 and animal180 subjects. Third, studies in isolated human airways9,10,88,39,120,121,132,139,148 and in airways from animal models of asthma50 show defective relaxant responses to beta adrenergic agonists.

Beta-adrenergic control of the airways involves sympathetic nerves, circulating catecholamines, and adrenergic receptors. Human airway smooth muscle, in contrast to pulmonary blood vessels, glands, and ganglia, is devoid of sympathetic innervation.118 Plasma catecholamines do increase in asthmatic subjects during exercise, but disagreement exists as to whether plasma levels of norepinephrine are sufficiently elevated to modify the severity of EIA.21,117 Although sympahtoadrenal activity as measured by catecholamine plasma levels during exercise in asthmatics appears similar to that in normal subjects,88,152 it is unknown whether the time course of catecholamine release is similar. With regard to receptors, beta-receptors of large and small human airway smooth muscle, airway epithelium, alveolar walls, and submucosal glands are entirely of the beta2 receptor subtype,20 which is consistent with functional studies that show that these receptors mediate relaxation of airway smooth muscle (fig. 1).150

In contrast, current evidence suggests that alpha adrenoceptor defects, i.e., increased number, sensitivity, and/or activity of alpha receptors, play, at best, a small role in the pathogenesis of airway reactivity of asthma (fig. 1). The specific alpha1 adrenergic antagonist prazosin, when inhaled, has little effect on resting airway tone in asthmatics, and only partially inhibits AIB in a subgroup of asthmatic subjects.18,20,23,25,149 Although this partial inhibition lends some credence to the idea that a defect in alpha adrenergic mechanisms is present in asthmatics, it seems unlikely to have a primary role.

A third nervous system called the nonadrenergic, noncholinergic system (fig. 1) has been demonstrated in human airways.119 The neurotransmitters involved have not yet been positively identified, although evidence to date favors neuropeptides. The majority of these suspected neuropeptides produce bronchoconstriction, although vasoactive intestinal polypeptide, peptide histidine methionine, atrial natriuretic peptide, vasopressin, and oxytocin are present in the lung and dilate airways.122 At present, no specific blockers to these neuropeptides are available, and the role of these neuropeptides and the importance of this dilator system in AIB, and asthma in general, remain to be elucidated.

**INCREASED PRESENCE OF INFLAMMATORY CELLS AND MEDIATORS**

The previously held view that mediators released from mast cells are the primary cause of asthma needs to be modified because several other cell types may play an equally important role in this phenomenon (fig. 1). Increased numbers of eosinophils are found in the airways of asthmatic subjects51,64,145 and eosinophils release a wide variety of inflammatory mediators. Among these are leukotriene C4 and platelet activating factor that cause constriction of airway smooth muscle,135 and major basic protein and eosinophil cationic protein that are toxic to and damage the epithelium.69 The role of the neutrophil is less clear, although indirect evidence suggests a role in EIA and in late phase responses in some asthmatics.91,93,109 Abnormalities in platelet function may also be involved in asthma,106 and platelet activation has been reported to accompany episodes of EIA.84

Inflammatory mediators may enhance non-specific bronchial responses in a variety of ways. They may increase mucosal permeability; modify sensory nerve endings, vagal activity, or cell receptor activity; interact synergistically with other mediators; produce cell infiltration; or alter smooth muscle contractility. Many cells, including bronchial mucosal and sub-mucosal mast cells, have been implicated as sources of inflammatory mediators. Transient increases in the osmotic environment can trigger both in vitro and in vivo mediator release,66,120 although the osmotic loads used in these studies may not be physiologically relevant. Basophils from atopic human9,146 and canine mast cells from the airway lumen77 show increased releasability when challenged in vitro. In fact, nasal lavages from individuals that respond to cold dry air exhibit increased osmolarity and elevated mediator concentrations when compared to nonresponders,142 and suggest that responses to cold dry air are caused by osmotic-induced mediator release.

Elevated levels of plasma histamine recorded after EIA suggest that mast cell activation may play a role in AIB;17,91 however, the reliability of this measurement has been questioned.79,105 Initially, neutrophil chemotactic factor (NCF) was proposed as a more sensitive marker of mast cell degranulation than changes in serum histamine.79,91,93,109 This is a controversial point and it is now argued that if NCF is not mast cell-derived, it is at least mast cell-associated, and its release is triggered from a second cell source by mast cell degranulation.21 NCF increases after EIA, and, in some individuals, after isocapnic...
hyperventilation. NCF activity is elevated after asthmatic subjects exercise breathing cold dry air, but remains unaltered following exercise with warm humid air, indicating that exercise per se does not trigger NCF release. "Fog"-induced bronchospasm is also associated with increases in plasma histamine and serum NCF suggesting the existence of shared pathways with AIB.

Disodium cromoglycate, a mast cell stabilizer, is relatively effective at attenuating various forms of airflow and "fog"-induced bronchospasm, and suggests that mediators are more important than cholinergic pathways in asthmatics that exhibit AIB. However, cromolyn also attenuates airway responses to hyperventilation with subfreezing air in normal subjects, which is surprising in light of the fact that normal individuals are assumed to have "stable" airway mast cells. Evidence does indicate that sodium cromoglycate also inhibits the afferent limb of the irritant reflex, thus differences between normal and asthmatic responses to airway cooling and drying may be due to the stimulation of an additional and separate nervous reflex operating only in asthmatic subjects. The interactions that occur in vitro in canine airway smooth muscle between cholinergic neurotransmission and prostaglandin mediators, if applicable in vivo, preclude further speculation as to cromolyn's site of action. However, these observations do not rule out the possibility that cromolyn stabilizes the membranes of other osmosensitive cells, tissues, or nerves. These data do suggest that hyperpnea and "fog" produce similar changes in the osmotic environment of the airways, and, in many cases, these changes are associated with mediator release, possibly originating from mast cells, as well as other inflammatory cells.

**Defects in Epithelial Function**

The airway epithelium is an important barrier to noxious agents by virtue of its impermeable nature and its mucociliary clearance capacity. However, increasing evidence indicates that the epithelium is a metabolically active tissue that can modulate the function of smooth muscle by the production and metabolism of inflammatory mediators, relaxant and constrictor factors, and chemotactants (fig. 1).

Epithelial cells are of particular interest because they are among the first airway cells to experience transient stimuli, whether related to changes in temperature or osmolarity. Epithelial cells from canine and human trachea convert arachidonic acid to lipoygenase-derived metabolites. Human, canine, rabbit, and guinea pig tracheal epithelium are involved in prostaglandin (PG) synthesis and release. Several recent papers document in vitro epithelial modulation of tracheal smooth muscle function, all suggestive of the existence of epithelial cell-derived mediators. The in vitro release and affects of these modulating factors appear to be heterogeneous along the bronchial tree. Thus, the bronchial epithelium appears to be an important source of inhibitory and excitatory substances.

AIB related epithelial desquamation of canine peripheral airways is significantly associated with increasing concentrations of prostaglandin D2 (PGD2), as assessed by bronchoalveolar lavage. This suggests that exposure to dry air causes dehydration and structural changes in the morphology of the respiratory epithelium phenomenons documented in guinea pigs. Dehydration is hypothesized to promote epithelial desquamation and may be accompanied by a concomitant increase in the osmosality of bronchial secretions. The resultant disruption of epithelial integrity or sudden change in extracellular fluid tonicity may directly trigger the release of a variety of cyclooxygenase and lipoygenase products. Eling et al. reported that isolated airway epithelial cells metabolize endogenous arachidonic acid in significant quantities via prostaglandin H synthetases and lipoygenases and that the metabolites formed, particularly PGD2, play an important role in controlling the volume and composition of airway secretions. Airway epithelia also produce leukotriene B4, an important chemotactic agent that influences the development of an airway inflammatory response. Epithelial cell damage occurs at all levels of the airways in asthmatic subjects, and may be prominent enough to expose epithelial nerves to non-specific stimuli. Thus, the epithelial abnormalities observed in asthmatics may lead by several mechanisms to the airway hyperresponsiveness of asthma. It is also possible that biochemical abnormalities in the absence of microscopic changes are present in cells of the bronchial epithelium of asthmatics in the early stages of the disease.

**Smooth Muscle**

An intrinsic defect in asthmatic airway smooth muscle itself has been proposed as the cause of increased in vivo airway sensitivity to airflow, to exercise, and to multiple pharmacologic agents. These include either enhanced responsiveness of the airway smooth muscle to constrictor substances or depressed activity of the muscle to relaxant substances.

Mechanical and biochemical properties of airway smooth muscle have been compared in unsensitized and sensitized animals. These studies are difficult to relate to human asthma because the models used lacked the non-specific airway hyperresponsiveness characteristic of the human syndrome. In vivo and in vitro comparisons of airway responsiveness have been performed in a few asthmatic patients and in the basenji-greyhound dog (table 1). These studies have all failed to demonstrate in vitro
increased mediator-induced sensitivity of isolated airway smooth muscle, although beta-adrenergic agonist relaxant responses appear to be impaired.

In vivo/in vitro correlations with temperature or osmotic stimuli are not yet available, but in vitro studies in human airway smooth muscle with hyperosmolar stimuli have shown little direct effect and no enhancement of histamine sensitivity.58 In addition, hyperosmotic-induced epithelial dependent relaxation (not constriction) of guinea-pig trachea has been demonstrated in vitro,108 and suggests that this osmotically induced factor may be important in modulating bronchoconstriction produced by the conditioning of dry air during periods of exertion in normal and asthmatic subjects. In combination, the above data suggest that in vivo osmotic challenge does not directly affect smooth muscle, but acts via the stimulation of other cells or tissues that can alter smooth muscle tone and reactivity.

In bovine and guinea pig tracheas,124 cooling depolarizes the cells and potentiates histamine-induced responses. Souhrada et al.133 showed that guinea pig tracheal segments respond to rapid cooling with an initial contraction. Although not emphasized, these same authors provide clear evidence of a sustained cold-induced relaxation following the initial transient constrictor response. In addition, rapid rewarming produced an initial transient relaxation followed by persistent constriction. More recently, Huang et al.80 demonstrated in vitro that constant cooling of guinea pig trachea decreases carbachol-induced constriction, and that low temperatures can alter arachidonate metabolism. Thus, airway smooth muscle responses to electrical stimulation, rapid cooling, and carbachol are consistent with the idea that cooling per se inhibits constriction. However, cold-induced hyperresponsiveness to histamine and rewarming-induced constriction suggest that cooling exerts an excitatory effect on airway smooth muscle. These discrepancies emphasize the point that in vitro data should be viewed with caution, particularly when comparisons are made with observations made in vivo.

**Potential Initiating Factors**

Respiratory heat exchange is primarily the result of evaporative water loss, and this accounts for the fact that cooling and drying are two inextricably linked stimuli that are associated with hyperpnea and cold air exposure. Airway cooling alone may initiate AIB,54,57,44,136 and the degree and rapidity of post-stress rewarming may contribute to the magnitude of the response.50,102 Proponents of this cooling hypothesis believe that the bronchovascular bed is similar to that of the skin, and that a rise in respiratory heat exchange causes bronchial vessels to constrict.100 More recent evidence suggests that this may not be the case.51 Even if the cooling that results from evaporative water loss is not amplified by a reduced influx of bloodborne heat, lower temperatures may stimulate thermosensitive receptors or smooth muscle directly. This, in combination with a hypothesized rewarming-induced hyperemia and edema,102 may produce airway obstruction.

Although no human data concerning the effect of cooling on airway blood flow is available, with the use of a canine model, Baile et al.11 have demonstrated that tracheal and central airway blood flow increases in response to cold air hyperventilation. In addition, these investigators examined whether cooling or drying of the airway mucosa was the primary stimulus evoking increased blood flow.12 They found that hyperventilation with warm dry air produced a greater increase in airway blood flow than hyperventilation with cold dry air, and suggested that drying was a more important stimulus than cold for increasing blood flow. Indeed, increased osmolarity in the pulmonary vasculature produces vasodilation.76 In addition, pretreatment with drugs such as aminophylline and atropine, or warm humidified air, has been hypothesized to ameliorate an osmotic stimulus by replacing the water lost from the bronchial mucosa via increased blood flow through the bronchial or pulmonary circulations.151

In contrast to the cooling hypothesis, there is evidence that changes in airway fluid osmotic pressure induced by evaporative water loss may trigger AIB.2,5,6,69,75,131 Although evaporative water loss and respiratory heat exchange occur simultaneously, changes in the osmotic environment result from evaporative water loss, and this may be the primary stimulus that initiates a cascade of events leading to airway obstruction. If alteration in airway fluid tonicity is the primary stimulus for AIB, then any intervention that produces a change in surface fluid osmolarity should produce AIB-like responses in the absence of cooling and drying. Studies using aerosolized hypo- or hypertonic solutions19,59,74,75,107,124,125,128,131 demonstrate that asthmatic subjects are considerably more sensitive to an osmotic challenge than normal individuals. The two studies including an isotonic aerosol control124,128 indicate that responses of asthmatic subjects to these solutions are
small. Responses to these hypo- and hypertonic solutions (i.e., fog-induced bronchospasm) are similar to AIB, and support the idea that any change in airway osmolarity may produce an airway constrictor response. Changes in airway fluid tonicity may damage airway epithelium and increase access to the paracellular space. Changes in intracellular tonicity, either directly or via reflex pathways, may initiate mediator release from osmosensitive cells. Such mediators stimulate smooth muscle constriction, inflammation, edema formation, and increased secretion, all of which are characteristic factors that may lead to acute airway obstruction in asthma (fig. 1).

The amount of water lost from surface fluid lining the respiratory tract as a result of dry air exposure is a controversial issue. In a recent study, calculations of water losses and airway surface fluid osmolarity during and after exercise failed to reveal any significant airway drying in either normal or asthmatic subjects. In contrast, other calculations suggest that sufficient water loss would occur to alter surface fluid osmolarity. These estimates should be interpreted with caution, because the assumptions made concerning water replacement, cumulative water losses, and, most importantly, the region over which water is actually lost, are not well defined. Drying of the canine bronchial mucosa retards mucociliary transport, and direct measurements of canine airway surface liquid and extravascular water loss in guinea pigs indicate that exposure to dry air can cause airway surface fluid to become hyperosmotic. However, ciliated epithelial cells in canine trachea respond asymmetrically to an osmotic stimulus, exhibiting a relatively greater osmotic conductivity on its serosal surface when compared to its mucosal surface. Thus, the bronchial mucosa may be relatively unaffected by the loss of periciliary fluid. Conversely, transient changes in intracellular osmolarity may occur via the basolateral cell membranes in response to changes in paracellular and extravascular fluid, and either osmotic changes in these fluids, or changes in water flux per se, may represent a critical stimulus in AIB. It is possible that periciliary or airway surface water volume remains relatively constant due to resupply from paracellular and extravascular sources, although calculations of water loss usually assume this is not the case. Thus, water lost from the airway surface may not accurately reflect either changes in intracellular water flux or transient changes in osmolarity, and the calculations of airway surface fluid losses used to estimate the strength of an osmotic stimulus may be misleading.

Definitive pulmonary function data concerning the independent effects of airway cooling and drying are unavailable for human subjects, and, until recently, neither respiratory water loss nor heat loss appeared to be the sole stimulus for bronchoconstriction. Recent experiments using an animal model of AIB to examine cold-induced bronchoconstriction provide additional data that confirm the results reported in an analogous study done in humans. However, the use of this model allowed the effect of cooling to be evaluated independent of drying, and has led to a strikingly different interpretation of those data: neither cooling nor rewarming per se initiates or enhances a constrictor response in this canine model of AIB. In fact, extreme cooling of the peripheral lung virtually abolishes AIB. Cooling may stabilize responsive cells or tissues, thus reducing mediator and neuronal stimulatory activity. Conversely, drying, through its effects on airway tonicity or fluid flux per se, may activate a variety of stimulatory pathways leading to airway obstruction (fig. 1). Breathing dry air does produce an acute loss of water from extravascular regions of the bronchial mucosa in guinea pigs, and airway drying increases airway responsiveness in these animals. Thus temperature appears to be a secondary modulatory factor, and the quantity of heat transferred across the mucosal surface may be useful as an indirect indicator of changes in the tonicity or flux of extravascular fluid.

Conclusions

We propose that AIB results from an imbalance in the responses of the pulmonary system to cooling and drying. Increases in minute ventilation produce a simultaneous decrease in airway temperature, and an increase in water loss from the airway bronchial mucosa. Airway drying, at this time by way of default, appears to be the primary stimulus that triggers the cascade of events resulting in AIB.

Although changes in the in vitro osmotic environment do not directly affect human tracheal smooth muscle, other in vitro studies demonstrate that mast cells, and, possibly, other airway cells, do respond to osmotic stimuli. Thus, airway drying may trigger the release of inflammatory mediators from osmosensitive cells. Also, evidence suggests that the epithelium produces relaxant factors that inhibit airway tone, and preliminary experiments in vitro suggest that exposure to dry air activates at least one of these epithelial-dependent processes. In contrast, cooling, via metabolic down regulation, may reduce mediator release and activity, receptor function, and/or cell and tissue responsiveness. It may even stimulate the release, or enhance the production or efficacy of a relaxing factor, as has been reported for endothelial-dependent relaxation in isolated rat aorta. Thus, intracellular water flux per se and/or alterations in the osmotic environment of mast cells, eosinophils, or epithelial cells may produce both excitatory and inhibitory effects on airway smooth muscle activity.

† Personal communication, M. Munakata.
In conclusion, we speculate that drying of the bronchial mucosa may inactivate an epithelial-dependent relaxant process, and simultaneously stimulate the release of bronchoactive mediators from osmoreactive cells. Cooling *per se* may counterbalance these various metabolic pathways. In fact, post-exercise airway rewaranging in asthmatic subjects has been reported to occur twice as fast as that in normal individuals, and this may be indicative of an impaired cold-associated regulatory process. If dry air inhibition of an endogenous relaxing factor does occur in asthmatic individuals, but is unaccompanied by a cold-induced down regulation, this imbalance between the effects of airway cooling and airway drying may initiate bronchoconstriction.

The authors wish to dedicate this paper in memory of the late Harold A. Menkes, M.D., Director and Professor of Environmental Physiology at The Johns Hopkins University. They also wish to thank Dr. Hall Downes, Professor of Pharmacology at Oregon Health Sciences University; Dr. Wayne Mitzner, Professor of Environmental Health Sciences at Johns Hopkins University; and Dr. Mitsuru Munakata, First Department of Medicine at Hokkaido University, for critically reviewing an early draft of this manuscript.

References

1. Adams F: The extant works of Aretaeus the Cappadocian. London, Sydenham Society, 1856, p 316
32. Chen WY, Horton DJ: Heat and water loss from the airways and exercise induced asthma. Respiration 54:305-313, 1977
of atropine on the potentiation of exercise-induced broncho-
37. Deal EC Jr, McFadden ER Jr, Ingram RH Jr, Jaeger JJ: Hy-
perpnea and heat flux: Initial reaction sequence in exercise-
38. Douglas JS, Dennis MW, Ridgway R, Bouhys A: Airway con-
striction in guinea pigs. Interaction of histamine and autonomic
39. Downes H, Austin DR, Parks CM, Hirshman CA: Comparison of
drug responses in vivo and in vitro in airways of dogs with and
without airway hyperresponsiveness. J Pharmacol Exp Ther
237:214–219, 1986
of the osmotic activation of basophils and human lung mast
41. Eggleston PA, Kagey-Sobotka A, Schleimer RP, Lichtenstein LM:
Interaction between hyperosmolar and IgE-mediated histamine
release from basophils and mast cells. Am Rev Respir Dis 130:
86–91, 1984
42. Eling TE, Danilowicz RM, Henkke DC, Sivarajah K, Yankaskas
JR, Boucher RC: Arachidonic acid metabolism by canine trache-
43. Enright PL, McNally JF, Sourdaha JF: Effect of lidocaine on the
ventilatory and airway responses to exercise in asthmatics. Am
44. Eschenbacher WL, Sheppard D: Respiratory heat loss is not the
sole stimulus for bronchconstriction induced by isocapnic hy-
45. Eschenbacher WL, Bethel RA, Boushey HA, Sheppard D: Mor-
phine sulfate inhibits bronchoconstriction in subjects with mild
asthma whose responses are inhibited by atropine. Am Rev Res-
pir Dis 130:563–567, 1984
46. Fanta CH, McFadden ER Jr, Ingram RH Jr: Effects of cromolyn
sodium on the response to respiratory heat loss in normal sub-
47. Findlay SR, Lichtenstein LM: Basophil "releaseability" in patients
48. Finney MJB, Anderson SD, Black JL: Effect of non-isotonic so-
solutions on human isolated allergic smooth muscle. Respir Physiol
49. Flavahan NA, Aarhus LL, Rimelle TJ, Vanhoutte PM: Respiratory
58:834–838, 1985
50. Flavahan NA, Vanhoutte PM: The respiratory epithelium releases
51. Flint KC, Leung KPB, Hudspith BN, Brostoff J, Pearce FL, Johnson
N McI: Bronchoalveolar mast cells in extrinsic asthma: A mechanism for the initiation of antigen specific broncho-
52. Fonkalarl EW, Sanchez M, Higashijima I, Arima E: A com-
parative study of the effects of dry vs. humidified ventilation
on canine lungs. Surgery 78:373–380, 1975
53. Foroni A, Mattoli S, Corbo GM, Polidori G, Ciappi G: Comparison of
bronchial responses to ultrasonically nebulized distilled water,
exercise, and methacholine in asthma. Chest 90:822–826, 1986
54. Freed AN, Bromberger-Barnea B, Menkes HA: Dry air-induced
constriction in the lung periphery: A canine model of exercise-
55. Freed AN, Kelly LJ, Menkes HA: Airflow-induced bronchospasm:
Imbalance between airway cooling and airway drying? Am Rev
56. Freed AN, Peters SP, Menkes HA: Airflow-induced broncho-
constriction: The role of epithelium and eicosanoid mediators.
57. Freed AN, Wang D, Menkes HA: Dry air-induced constriction:
Effects of pharmacological intervention and temperature. J Appl
58. Frossard N, Muller F: Epithelial modulation of tracheal smooth
muscle responses to antigenic stimulation. J Appl Physiol 61:
1449–1456, 1986
59. Fuller RW, Collier JG: Sodium cromoglycate and atropine block
the fall in FEV1, but not the cough induced by hypotonic mist.
60. Gilbert IA, Fouke JM, McFadden ER Jr: Heat and water flux in
the intratracheal airways and exercise-induced asthma. J Appl
Physiol 63:1681–1691, 1987
61. Gilbert IA, Fouke JM, McFadden ER Jr: Intra-airway thermodynamics
during exercise and hyperventilation in asthmatics. J Appl Physiol
64:2157–2174, 1988
D: Cytotoxic properties of the eosinophil major basic protein.
J Immunol 123:2925–2927, 1979
63. Godfrey S: Controversies in the pathogenesis of exercise-induced
64. Godard P, Chaintreuil J, Damon M, Coupe M, Flandre O, Crastes
de Paulet A, Michel FB: Functional assessment of alveolar mac-
rophages: Comparison of cells from asthmatics and normal sub-
responsiveness of human asthmatic bronchus to carbachol, his-
tamine, β-adrenoceptor agonists and theophylline. Br J Clin
Pharmacol 22:659–676, 1986
66. Gravelyn TR, Pan PM, Eschenbacher WL: Mediator release in an
isolated airway segment in subjects with asthma. Am Rev Respir
Dis 137:541–546, 1988
67. Griffin MP, Fung KF, Ingram RH Jr, McFadden ER Jr: Dose-
response effects of atropine on thermal stimulus-response re-
68. Griffin MP, McFadden ER Jr, Ingram RH Jr, Pardee S: Con-
trolled-analysis of the effects of inhaled lignocaine in exercise-
induced asthma. Thorax 37:741–745, 1982
69. Hahn A, Anderson SD, Morton AR, Black JL, Fitch KD: A re-
interpretation of the effect of temperature and water content of
the inspired air in exercise-induced asthma. Am Rev Respir Dis
130:575–579, 1984
70. Hauge A, Gunnar B: Blood hyperosmolality and pulmonary vas-
71. Hay DWP, Farmer SG, Raeburn D, Robinson VA, Fleming WW,
Fedan JS: Airway epithelium modulates the reactivity of guinea-
pig respiratory smooth muscle. Eur J Pharmacol 129:11–18,
1986
72. Hay IFC, Harmes K, Higenbottam TW: Water loss from the lung,
the effects of eucapnic hyperventilation of cold air. Clin Sci
68:45P–46P, 1985
73. Heaton RW, Henderson AF, Gray BJ, Costello JF: The bronchial
response to cold air challenge: Evidence for different mecha-
nisms in normal and asthmatic subjects. Thorax 38:506–511,
1983
74. Higenbottam T, Borland C, Barber B, Chamberlain A: Pulmo-
ney epithelial permeability after inhaled distilled water “fog.”
Chest 87:1565–1565, 1985
75. Higenbottam T, Stokes T, Jamieson S, Hill L: A comparison of ex-
ercise, hyperventilation with cold air and warm air, and the
inhalation of “fog” in the provocation of asthma. Eur J Respir
Dis 64:421–423, 1983
76. Hirshman CA: Airway reactivity in humans. ANESTHESIOLOGY
58:170–177, 1983
77. Hirshman CA, Austin DR, Kettelkamp NS: Enhanced bron-


117. Pichurko BM, Sullivan B, Porcelli RJ, McFadden Jr ER: Endog-


