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Asthma and inflammation

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Concepts on the pathogenesis of asthma have changed considerably during the past few years. In the early part of this century, experimentalists were greatly impressed with the asthmatic symptoms produced in animals by drugs, such as muscarine, pilocarpine, and physostigmine. Atropine, hyoscyamine, and chloroform abolished these effects, and for many years, these substances were used to treat asthma attacks. The classic work on histamine by Sir Henry Dale and other investigators suggested a clear interrelationship between chemical mediators, anaphylaxis, allergy, smooth muscle contraction, and asthma. Thus, the asthmatic paroxysm was regarded essentially as spasm of bronchial muscle, although "vascular turgescence" of the bronchial mucus membrane and increased secretion of mucus glands were also recognized. The acute asthma attack was believed to be associated with excessive vagal discharges triggered by peripheral irritation or centrally from cerebral influences.

Until the 1950s, the mainstay of treatment for asthma was the antispasmodic agents, that is, adrenaline, atropine, and theophylline. Corticosteroids

Abbreviations used

EOS:	Eosinophil
BAL:	Bronchoalveolar lavage
NCA:	Neutrophil chemotactic activity
Ag:	Antigen
MBP:	Major basic protein
ECP:	Eosinophil cationic protein
PC ₂₀ :	Provocative concentration causing a 20% fall in FEV ₁
PAF:	Platelet-activating factor
ICAM-1:	Intercellular adhesion molecule-1
LPR:	Late-phase reaction
Fc _R :	Fc ₁ receptor
GM-CSF:	Granulocyte macrophage-colony-stimulating factor
MAb:	Monoclonal antibody
IFN:	Interferon
ASA:	Acute severe asthma
HLA:	Human leukocyte antigens
VLA:	Very late activation
HMW:	High-molecular-weight
SCG:	Sodium cromoglycate
LFA:	Lymphocyte function-associated antigen
mRNA:	Messenger ribonucleic acid
LAR:	Late asthmatic reaction
Th:	T helper
LTC ₄ , LTD ₄ , LTB ₄ :	Leukotrienes C ₄ , D ₄ , and B ₄
IL:	Interleukin
PGD ₂ :	Prostaglandin D ₂

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were introduced very cautiously. At first they were reserved only for the extreme, life-threatening, variants of the disease. Indeed, initially, there was considerable controversy as to the precise indications for these agents in "prevention" of day-to-day asthma. Several years of clinical experience with corticosteroids raised two important questions. The first was whether the response to prednisolone, which was often dramatic, was consequent to its anti-inflammatory effects or was due to some other property of glucocorticosteroids. The second question regarded the state of the bronchi *between* attacks. It became clear that the bronchi were not "normal" in the sense that corticosteroids could often "open up" the airways and appreciably increase function, even in the ostensibly well-controlled patient. Thus, it became clearer that, for many patients, asthma was essentially a *chronic disease* with intermittent acute exacerbations. In other words, spasm and paroxysm appeared to be superimposed on airways that were already chronically inflamed and, as a consequence, partially obstructed. Thus, the notion that asthma is simply bronchospasm occurring in isolation has largely been discarded. This major modification in our thinking has had important implications in managing the disease.

What is the nature of the inflammatory response in bronchial asthma and how do the various inflammatory cells and their products contribute to the pathologic features of the disease? These issues are addressed in this article.

INFLAMMATION AND INFLAMMATORY CELLS

Inflammation is the response of vascularized tissue to injury and is usually beneficial since it serves to resolve and repair the effect of damage. The factors that initiate inflammation, like those of cell injury, are diverse and include infectious agents (bacteria, viruses, and parasites), physical agents (burns, radiation, and trauma), chemical agents (drugs, toxins, and industrial agents), ischemic injury to tissues, and immunologic reactions, such as allergy and autoimmunity. The histopathologic features of inflammation consist of changes in blood flow and caliber of small blood vessels followed by an increase in vascular permeability, the formation of an inflammatory exudate, and the escape of leukocytes from the blood into the extravascular spaces. Acute inflammation is of short duration and characterized by exudation of fluid with plasma proteins (edema) and emigration of granulocytes from the microvasculature. In contrast, chronic inflammation has a longer time span and is more cellular with granulocyte emigration being accompanied by a dense infiltration of lymphocytes and mono-

cytes/macrophages together with proliferation of blood vessels and connective tissue. In certain specialized circumstances, such as atopic allergic inflammation and asthma, increases in the numbers of EOSs are also characteristic. Both acute and chronic inflammation are associated with some degree of fibrin deposition with platelet adherence and the release of platelet products. Basophils are also inflammatory cells and are prominent in various forms of delayed-type hypersensitivity. They are also found in the upper airways in allergic rhinitis, but at the present time there is no conclusive evidence that the basophil participates in pathologic processes in the lung. Thus, the cells migrating from the blood vessels that have been clearly identified in airway inflammation include the neutrophil, EOS, lymphocyte, and macrophage. Platelets may contribute to the reaction, but their ability actively to emigrate from the bloodstream remains controversial. Certain resident tissue cells, such as mast cells and epithelial cells, probably participate, as does the fibroblast. Inflammation at all mucosal surfaces, including the airways, has two additional important features: mucus hypersecretion and shedding or denudation of the epithelial surface.

These inflammatory cells produce a wide range of inflammatory mediators that include PAF, leukotrienes, histamine, and cytokines. These agents contribute not only to the development of the inflammatory response but also to its modulation by feedback mechanisms. Cellular events in the bronchial mucosa are also influenced by neuropeptides secreted by neuroendocrine tissue in the airways.

It is very unlikely that one cell, or one mediator, will explain totally the mechanisms in asthma and attendant bronchial hyperreactivity but rather that the combined effects of a number of cells and their products are required for the observed effects.

Pathologic evidence for inflammation in asthma

Until recently, pathologic studies in asthma were largely confined to tissues obtained from patients who had died in status asthmaticus. In asthma deaths, certain features appear to be typical. Histologically, there is loss of surface-lining epithelium, thickening of the reticular layer beneath the basal lamina of the epithelium, dilatation of bronchial blood vessels, and mucosal edema and hypertrophy of both submucosal glands and bronchial smooth muscle. A dense infiltration of inflammatory cells is also present in both the occluding plug and airway mucosa.¹⁻³ The intense infiltration of EOSs and deposition of EOS products in and around the bronchial epithelium is a particularly prominent feature.⁴ There are also large numbers of

lymphocytes and macrophages. Neutrophils are also sometimes present at necroscopy. The events accompanying airway narrowing in asthma are diagrammatically represented in Fig. 1.

With the continuing application of bronchial biopsy and "bronchial" lavage via the fiberoptic bronchoscope as an investigative tool in asthma, it has become clear that many of the inflammatory and structural changes that are observed in asthma deaths are also a feature of mild on-going, well-controlled disease. For instance, it has been demonstrated that subjects with asthma shed significantly higher numbers of epithelial cells into BAL fluid than control subjects and that there was a significant correlation between epithelial cell count and bronchial responsiveness.^{5,6}

Eosinophilia was also a feature of the histopathology of biopsy specimens from subjects with mild asthma⁷ as well as from BAL.⁵ The association of EOSs and their products with lung function is discussed below. Neutrophils (as demonstrated by neutrophil elastase-positive cells) were not increased in biopsy specimens from volunteers with asthma when volunteers were compared to control subjects (subjects with atopic rhinitis and normal individuals).⁷ In contrast, an increase in the number of activated lymphocytes, identified either as irregular, atypical lymphocytes by transmission electron microscopy⁸ or IL-2 receptor-positive cells, as demonstrated by immunohistochemistry,⁷ were a constant finding in biopsy specimens in asthma.

Recently, immunohistochemical and electron microscopic studies by Roche et al.⁹ and Jeffery et al.⁸ have demonstrated that there is not true thickening of the basement membrane in asthma but deposition of reticular collagen or subepithelial fibrosis. These findings suggest that fibroblast activation rather than bronchial epithelial cell dysfunction might account for this deposition of reticular material.

Although our knowledge of the basic on-going asthma is increasing, the dynamics of these processes are still unclear. For instance, what is the sequence of cell emigration and is this different from that observed in inflammatory processes in other diseases in other organs and tissues? How does this inflammatory process resolve? What is the sequence of the structural changes? Are the changes in the airways of subjects with asthma the same or is there heterogeneity of the lesions?

Changes in the microvasculature

It is virtually certain that microvascular leakage occurs in asthma of any severity not only because of the histopathologic findings but also because sputum^{10,11}

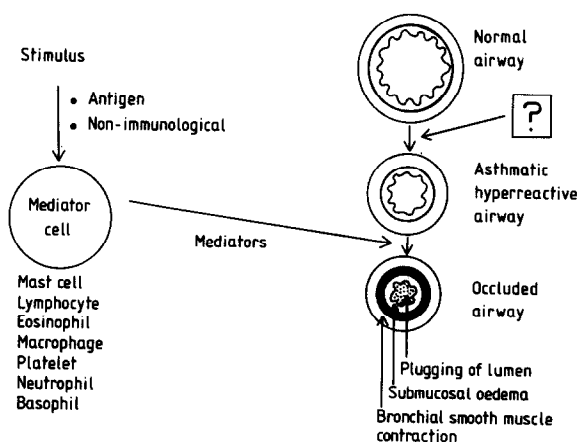


FIG. 1. A hypothetical scheme that attempts to explain how the airways in asthma are obstructed. *Right*, ignorance on the *inception* of asthma is highlighted by the question mark. However, asthma is believed to be induced by the actions of mediators on the hyperreactive asthmatic airway. Partial (and sometimes total) occlusion of the airway results from the combination of bronchial smooth muscle contraction, submucosal edema, and plugging of the lumen with mucus, cells, and cell debris. Mediators are derived from mediator cells (either from the granules or membrane) and the likely candidates (i.e., mast cells, EOSs, etc.) are listed. Resident cells, such as bronchial epithelial cells and fibroblasts, should probably also be added to this list. Mediator cells can be triggered either by Ag, that is, IgE-dependent mechanisms, or non-immunologically, for example, after exercise-induced asthma.

and BAL fluid from subjects with asthma contain elevated concentrations of albumin.^{12,13} The amount of albumin in BAL fluid is also increased after exposure to inhaled Ag.¹⁴ Furthermore, permeability of the bronchial mucosa to an aerosol of ^{99m}technetium-diethylenetriamine pentaacetic acid was increased in asthma.¹⁵

Many of the mediators implicated in asthma are known to cause microvascular leakage of postcapillary venules. These include histamine, bradykinin, LTC₄, LTD₄, and PAF.¹⁶⁻¹⁹ In addition, stimulation of the vagus nerve or injection of capsaicin, via release of sensory neuropeptides, such as substance P, cause microvascular leakage in rodents.²⁰ Furthermore, mediators that increase bronchial blood flow might be expected to exaggerate leakage in airways of subjects with asthma. Edema, as a result of increased capillary permeability, may have several sequelae relevant to asthma. These include a contribution to narrowing of small airways, epithelial shedding, the formation of mucus plugs, inhibition of mucociliary clearance, and, by providing a rich source of plasma proteins, substrate for complement-derived anaphylatoxins and

kinins. To the extent that edema represents an alteration in permeability, it may also contribute directly to alterations in responsiveness by allowing greater (or different) agonist penetration to the smooth muscle.

Neutrophils

The accumulation of neutrophils into the airways under conditions of inflammation has the potential to result in significant tissue damage. This cell type is associated with tissue injury in many inflammatory conditions.²¹ The mechanisms by which this injury may occur include the release of oxygen metabolites, proteases, and cationic materials. Additionally, the neutrophil is a potential source of a wide variety of mediators, including potent lipid mediators, such as prostaglandins, thromboxanes, LTB₄, and PAF, which may then contribute to airway responses and/or exacerbation of the inflammatory response.

The evidence that neutrophils by themselves play an important role in asthma and bronchial hyperresponsiveness is controversial. On the one hand, a number of studies in experimental animals, as well as control models of asthma in man, indicate that neutrophils may play a part early in the asthma process. Neutrophils appear to be a "normal" resident of larger airways both in normoresponsive and hyperresponsive individuals. Wardlaw et al.⁵ found a high percentage of neutrophils in the bronchial wash of nonatopic control subjects and hay fever sufferers, as well as in subjects with mild asthma. The numbers were approximately equal in all groups and considerably higher than numbers observed in bronchoalveolar wash. In fact, neutrophils accounted for almost 50% of the total cell count in bronchial (as opposed to bronchoalveolar) washes in normal subjects. Similar findings were obtained by Azzawi et al.⁷ who found comparable numbers of neutrophil elastase-positive cells in mucosal biopsy specimens from subjects with asthma and control subjects. It must be remembered that neutrophils in subjects with asthma may demonstrate a different degree of activation or stimulation in comparison with neutrophils of normal subjects. For instance, numerous studies indicate that peripheral blood neutrophils become "activated" after allergen- and exercise-induced early and late-phase asthmatic responses.²²⁻²⁵ Activation was assessed by increased membrane expression of complement receptors and enhanced cytotoxicity for complement-coated targets. Such observations suggest that the circulating neutrophils have been exposed to some stimulus. However, many of the currently known stimuli for neutrophils are not specific for this cell type; therefore, activation of other inflammatory cells may also result from the same circumstances.

Significant increases in the percentage of neutrophils in BAL and bronchial mucus have been observed in subjects experiencing LPRs after bronchial challenge.²⁶ Comparable observations were made in BAL during LPRs in sensitized subjects challenged with toluene diisocyanate, in which it was found that increases in neutrophils, as well as EOSs and lymphocytes, were inhibited by prior administration of oral prednisolone.¹³ In contrast, BAL neutrophilia was not a feature of late reactions elicited by plicatic acid in red cedar asthma.²⁷

The elaboration of an HMW NCA into the circulation of patients after allergen- or exercise-induced early and LPRs is well documented.²⁸⁻³¹ HMW NCA was associated with molecules having a molecular size of approximately 600 kd and a near neutral isoelectric point. This activity has recently been identified from the serum of subjects with asthma admitted to hospital with ASA ("status asthmaticus").³² The molecular size of NCA in ASA was heterogeneous, that is, 800, 600, and <20 kd. When peripheral blood mononuclear cells from patients with ASA were cultured in serum-free medium, a low-molecular-weight NCA was also detected in the supernatant.³³ Present evidence suggests that this may be derived from lymphocytes and/or monocytes and that it is possibly related to IL-8.³⁴⁻³⁸ The nature of HMW serum factor remains unresolved.

Convincing evidence suggesting that neutrophils are capable of altering airway functions comes from animal experiments. The cell has been firmly implicated in ozone-induced and Ag-induced hyperreactivity in dogs,^{39,43} in Ag-induced LPRs, and hyperresponsiveness in rabbits^{41, 44} and in sheep exposed to both endotoxin^{45, 46} and Ag.⁴⁷ Rabbits demonstrate increased responsiveness when airway inflammation is induced with phlogistic fragments of C5, and this too was dependent on neutrophils.⁴⁸ The requirements for granulocytes (especially neutrophils) in these experiments has been established by association (lavage and histology), depletion studies (e.g., nitrogen mustard), and, more convincingly, by depletion followed by selective repletion with enriched populations of purified neutrophils.⁴¹ Furthermore, supernatants prepared from phagocytosing neutrophils *in vitro* induced hyperreactivity when they were nebulized into the airways of rabbits,⁴⁹ whereas the supernatants from EOSs did not. The active agents in this model are yet to be identified. By contrast, in the guinea pig, there was also a sevenfold increase at 6 hours and 17-fold increase at 17 hours in neutrophils in BAL in a model of late-phase and "late-late" phase bronchoconstriction.⁵⁰ Nedocromil sodium blocked the late reaction and subsequent EOS infiltration in BAL but did not affect the neutrophil infiltration. This finding sug-

gested that in the late-phase and "late-late" phase, neutrophil infiltration is less critical for the development of airway obstruction in this species.⁵¹

Whether or not the neutrophil participates in the functional alterations associated with asthma remains an open question. The frequent recovery of neutrophils from BAL of patients with asthma,^{52, 53} the presence of neutrophils in pathologic sections of asthmatic airways,^{54, 55} and the ability of human neutrophils to alter airway function suggest that they probably do participate.

EOSs

There is strong circumstantial evidence that suggests that EOSs are important proinflammatory cells in the asthma process. It is well-known that a blood and sputum eosinophilia is often, but not invariably, found in association with most forms of asthma. A blood eosinophilia accompanied LPR but not single early asthmatic responses, and there was an inverse correlation between the blood EOS count and the degree of nonspecific bronchial hyperreactivity as measured by the methacholine PC₂₀.⁵⁶ Frick et al.⁵⁷ have extended these findings to demonstrate that the proportion of hypodense EOSs in peripheral blood is elevated in such patients and better reflects the severity of asthma than the total EOS count. In sensitized monkeys, an airway eosinophilia was induced with Ag-coated Sepharose beads. This correlated with an increase in airway hyperresponsiveness.⁵⁸

The accumulation of EOSs and EOS products MBP, ECP, and EOS-derived neurotoxin have been observed in BAL during allergen-induced LPRs.^{26, 59, 60} Similar observations were made in red cedar asthma in which it was observed that plicatic acid inhalation elicited a BAL eosinophilia together with sloughing of bronchial epithelial cells.²⁷ In a placebo-controlled, double-blind study, SCG was demonstrated to suppress the local accumulation of EOSs in bronchial mucus and BAL fluid and demonstrated that these reductions in lung EOSs were related to clinical improvement.⁵²

As already mentioned, EOSs are also very prominent cells in many of the histopathologic sections obtained after death from asthma.^{2, 3} In fact, the pathology is often termed "chronic eosinophilic desquamative bronchitis." MBP was prominent in the bronchial wall and in the mucus plugs of virtually all these patients, even though only a few intact EOSs were observed by routine light microscopy.⁴ MBP concentrations were also elevated in the sputum from subjects with asthma. Beasley et al.⁶ found that, in bronchial biopsy specimens from subjects with mild asthma, the presence of EOSs in the lamina propria was confined to subjects with asthma, being absent in control sub-

jects, and that these cells demonstrated morphologic features of activation. Azzawi et al.⁷ demonstrated a significantly high number of EG2 positive cells in subjects with atopic asthma. EG2 recognizes a determinant of the cleaved and secreted form of the ECP.

ECP and MBP are both cytotoxic to the respiratory epithelium⁶¹ in vitro and in experimental animals, and both may contribute to the denudation of the epithelium observed in asthma. Subjects with asthma with airway hyperreactivity (PC₂₀, <4 mg/ml) had significant elevations in the EOS count and concentrations of MBP in BAL fluid.⁵ Furthermore, there were significant correlations between the amount of MBP recovered and the percentage of EOSs. These changes were even more marked when subjects with asthma with airway hyperreactivity were compared with subjects with normoreactive airways. There were inverse correlations between the PC₂₀ and the percentage of EOSs and epithelial cells and the amount of MBP in BAL. This study and that by Lam et al.²⁷ clearly suggested that bronchial hyperresponsiveness was associated with increased amounts of EOSs and their products. It is also consistent with the suggestion that the responsiveness is secondary to epithelial cell damage mediated through the basic proteins of the EOS. However, this suggestion presupposes that the hyperresponsiveness is caused by epithelial damage and that EOSs have a particular ability to induce this damage. Both of these findings may be the case but need to be clearly demonstrated. Evidence from Flavahan et al.⁶² adds support to this hypothesis. These investigators demonstrated that the increase in reactivity of in vitro preparations of tracheal rings in the presence of MBP was dependent on the presence of the epithelium. This finding suggests that the association between nonspecific bronchial hyperresponsiveness and MBP in BAL may be due to the effect of MBP on epithelial cells that may then affect the reactivity of the smooth muscle.

Direct intratracheal instillation of purified EOS granule proteins was recently undertaken in primates. MBP caused a dose-related increase in airway responsiveness to inhaled methacholine,⁶³ whereas the other granule-derived basic proteins were ineffective.

In addition to the basic proteins of the EOS granule, membrane phospholipid-derived mediators may also play a role in the pathogenesis of asthma. EOSs produced considerable quantities of LTC₄ after ionophore-,⁶⁴⁻⁶⁶ IgG-,⁶⁷ and IgE-dependent stimuli,⁶⁸ and small elevations in LTC₄ were noted in BAL in "baseline, resting" asthma,⁶⁹ as well as in the LPRs when fluid from diluent challenge was compared with fluid obtained from allergen challenge.²⁶

EOSs have the capacity to generate comparable

quantities of PAF^{70, 71} to that produced by neutrophils. PAF may be of particular relevance to asthma because of its ability to cause vasodilation and increased vascular permeability, to induce EOS chemotaxis⁷² and adherence to endothelial cells,⁷³ and to enhance mucus secretion and increase bronchial hyperresponsiveness after inhalation in man.⁷⁴ However, there are no convincing studies to date of PAF elaboration associated with clinical asthma.

The mechanism of recruitment of the EOS, in preference to the neutrophil, to the human asthmatic airway still needs to be explained. Is it merely a response to a larger stimulus, a less efficient removal process, or are the stimuli (signal) somehow different or more prolonged in comparison with stimuli in other inflammatory reactions? PAF is a potent chemotactic factor for EOSs but is also effective *in vitro* at evoking directional neutrophil migration. It is of particular interest that PAF induced a local eosinophilia after intracutaneous administration to atopic but not non-atopic subjects.⁷⁵ Similarly, reversed anaphylaxis with anti-IgE evoked a local skin eosinophilia in atopic subjects only.⁷⁶ Nevertheless, it appears likely that *in vitro* chemotaxis is not a true model of cell accumulation *in vivo* since it does not take into account the requirement for the chemoattractant to cross the vessel wall, the special requirements of cell adhesion to endothelial cells, the process of emigration itself, nor the metabolism that any chemotactic signal might be subjected to in the tissue.

It is now appreciated that T cell-derived products that play a vital role in EOS maturation also affect the mature cell. For instance, both GM-CSF and IL-5 activate mature EOSs in terms of increased cytotoxicity and oxidative metabolism and prolong the life of EOSs *in vitro*.^{77, 78} Recently, it was demonstrated that IL-5 caused hyperadherence of human EOSs, but not neutrophils, through mechanisms dependent, at least in part, on the CD11/18 family of adhesion glycoproteins.⁷⁹ The ligand for one of these adhesion glycoproteins (LFA-1) is ICAM-1.⁸⁰ ICAM-1 is expressed on inflamed endothelium and epithelium.⁸¹ It was recently demonstrated that in a primate model of asthma a MAb to ICAM-1 attenuated both airway EOSs and bronchial hyperresponsiveness.⁸² This finding indicates that ICAM-1 may play a central role in the airway inflammation of asthma and suggests that maneuvers designed to decrease adhesion of EOSs (and possible other inflammatory cells that express LFA-1, such as the lymphocytes⁸³) may be a useful therapeutic approach.

Other factors, such as IL-1, also alter the endothelium to render it more adherent for granulocytes. Furthermore, IL-1-induced human endothelial cell su-

permatants prolong EOS survival, an effect that was inhibited by glucocorticosteroids.⁸⁴

Recruitment and activation of EOSs is strongly inhibited by corticosteroids, an effect that could explain the efficacy of these drugs in modifying late-phase bronchoconstriction. This finding has to be tempered by the controversial effect of corticosteroids on bronchial hyperresponsiveness⁸⁵ and the common clinical experience of asthma persisting long after the peripheral blood eosinophilia has been corrected. Theophylline, which has little effect on bronchial hyperresponsiveness, potentiates *in vivo* EOS activation, as revealed by increases in superoxide anion production.⁸⁶

Mast cells and basophils

In human lung, mast cells are located in the lumen of the airways (in which they can be recovered by BAL), in the bronchial epithelium, and in the submucosa as well as the lung parenchyma. Two types of human mast cells termed T (tryptase-positive and chymase-negative) and TC (tryptase-positive and chymase-positive) mast cells have recently been described, based on differences in neutral protease content.⁸⁷ Most human bronchial mucosal mast cells contain tryptase as their major neutral protease. In this regard they resemble the mucosal rather than the connective tissue-type cell observed in rodents. Basophils have not been identified in bronchial pathology, although they probably exist as they do in most other organs. Preliminary studies indicate that basophils can be recruited from lavaged isolated bronchi challenged with Ag.

Current evidence suggests that the early allergic asthmatic reaction is predominantly mast cell mediated. The immediate response to inhaled allergens in atopic subjects (accompanied by elevations in plasma histamine) is rapid in onset and easily prevented by prior inhalation of β_2 -adrenoreceptor agonists (i.e., salbutamol) or SCG.⁸⁸ (In these situations the drugs are assumed to act on the mast cell [as well as smooth muscle], although as far as SCG is concerned, *in vitro* data do not support this view.⁸⁹) Corticosteroids administered during a period of time also attenuate the immediate reaction,⁹⁰ possibly by depletion of mast cells in the mucosa.⁹¹⁻⁹² After allergen challenge in atopic individuals, there are elevations in plasma histamine⁹³ and in both histamine and mast cell tryptase in BAL.^{5, 94} This finding occurs within minutes of challenge, and urinary secretion of a major catabolite, *N*-methylhistamine, is increased for a few hours after the challenge.⁹⁵ Mast cells recovered from the airways by lavage within the first 15 minutes of allergen challenge have all the morphologic features

of noncytotoxic degranulation.^{61, 96} Human lung mast cells also elaborate LTC₄, PGD₂, various chemotactic peptides, proteolytic enzymes, and proteoglycans. However, the pathophysiologic role of these lipid mediators, proteolytic enzymes, and proteoglycans is as yet unknown.

Mast cells are present in various stages of degranulation in subjects with asthma but not in control subjects, which supports the suggestion that degranulation and mediator release occur continuously within the bronchial mucosa of subjects with atopic asthma.⁶ Activation of mast cells as a pathogenetic mechanism of immediate bronchoconstriction is not limited to allergen exposure, since there is some evidence that it is also involved in asthma provoked by exercise, cold air, and hyperventilation.⁹⁷ In ongoing, day-to-day asthma, there is an inverse correlation between the methacholine PC₂₀ and the percentage of mast cells in BAL⁵ and the amounts of histamine in BAL fluid.⁹⁴ Furthermore, subjects with asthma with airway hyperreactivity have significant increases in spontaneous histamine release from BAL mast cells.

What is the role of the mast cell in LPRs, airway reactivity, and ongoing asthma? More than a decade ago it was demonstrated that F(ab)₂ anti-IgE, when it was injected into the skin, produced an LPR that had many of the histopathologic features of allergen-induced LPR. For this reason, it was hypothesized that mast cells were essential for the LPR and that mast cell-derived chemotactic factors accounted for the subsequent infiltration of EOSs, neutrophils, and basophils. More recently, a similar dependency on IgE was demonstrated for the induction of an aeroallergen-induced LPR in the airways of rabbits (inflammation and bronchoconstriction).⁹⁸ However, these findings do not prove the involvement of mast cells, since the anti-IgE or Ag may also have interacted with macrophages or lymphocytes through IgE on their Fc_εR II; these cells, in turn, may have contributed to the LPR. The airway LPR was inducible in rabbits passively sensitized with IgE-containing serum, further suggesting a so-called "type I allergic reaction." In contrast, evidence is now accumulating that the LPR (mainly from the skin, and to a lesser extent in the lung) is associated with the presence of lymphocytes and may therefore include elements of delayed-type hypersensitivity (type IV reactions) (see below).

It has recently been reported that Fc_εR I receptor-mediated activation of murine mast cells results in the production of GM-CSF and IL-3.⁹⁹ mRNA for several other cytokines, including IL-5 and IFN-γ, has also been identified in similarly activated mast cell clones.¹⁰⁰ These cytokines, previously believed to be secreted only by lymphocytes and mononuclear

phagocytes, have the ability to recruit, prime, and activate neutrophils, monocytes, and EOSs. Their elaboration by mast cells in response to allergen would enable the local defence system to become self-regulated and could also provide a mechanism by which the mast cell could participate in the LPR.

Thus, the evidence that mast cells are involved in immediate bronchoconstriction to immunologic and nonimmunologic stimuli is strong. The evidence that mast cells play an essential role in the LPR is debated, and there is little evidence for or against the suggestion that the products of this cell are important in ongoing, day-to-day, chronic asthma. Mast cells may be involved in inflammation in general and are found in association with a variety of pulmonary pathologies. Indeed, the most dramatic increases in mast cell numbers in the lung are found in fibrotic conditions,¹⁰¹ although, as noted above, the presence of the cell does not necessarily indicate what role it may play in pathophysiologic processes.

Monocytes and macrophages (mononuclear phagocytes)

The role of mononuclear phagocytes as accessory, Ag-presenting cells is well established; it is reasonable to assume that in health and disease such cells are present in and around the bronchi in which they process Ag and present it to local T cells in a major histocompatibility complex, class I or class II-restricted fashion. Experiments in rodents suggest that, under normal circumstances, alveolar macrophages play an important role in attenuating local immunity in the bronchial mucosa by preventing optimal Ag presentation by dendritic cells to T cells.¹⁰² Ia⁺ dendritic cells have been clearly demonstrated in human¹⁰² and experimental animal bronchial epithelium.¹⁰³ It has been suggested that in asthma there may be an escape from local immune tolerance when susceptible individuals are repeatedly exposed to allergen.

Most cells recovered from BAL in normal as well as in subjects with asthma are macrophages. These cells contain functional IgE receptors (Fc_εR II),^{104, 105} and the numbers of these IgE-bearing cells are substantially higher in atopic subjects with asthma than in normal control subjects.¹⁰⁶ Macrophages have the capacity to produce a wide range of lipid mediators, including eicosanoids from the lipoxygenase and cyclooxygenase pathways, as well as PAF. Mononuclear phagocytes also make and secrete an array of proteins and peptides, such as IL-8, C5a, platelet-derived growth factor, tumor necrosis factor, GM-CSF, IL-1, and various partially characterized histamine-releasing factors. These all have biologic activities that

may contribute to the airway reactions. It would be very surprising if this cell type did not participate, at least in part, in airway responses to inhaled allergens. Appreciable amounts of β -glucuronidase were recovered free in BAL,¹⁰⁷ although the macrophage is only one potential source of this marker for lysosomal enzyme secretion; a substantial increase in the number of macrophages has been reported after allergen challenge.⁶⁰ This increase appears to be due to the migration of monocytes into the lung because most of the increase can be accounted for by peroxidase-positive cells (a characteristic feature of monocytes compared with that of alveolar macrophages).

Lung macrophages are also activated in the LPR after allergen challenge, as revealed by an increase in the number of complement rosettes.²⁶ Subjects with chronic severe asthma who are relatively unresponsive to corticosteroids have increased numbers of circulating activated monocytes.¹⁰⁸ Furthermore, an as yet unidentified monocyte-derived, neutrophil-activating factor has been identified from corticosteroid-resistant asthma.¹⁰⁹

These observations provide only circumstantial support for the mononuclear phagocyte as a player in the pathogenesis of asthma. Nevertheless, the cell type is pluripotent and is involved not only in most inflammatory reactions but also in the afferent arm of the immune response as well. Histologically, the inflammatory lesions in asthma include mononuclear phagocytes, and they may be presumed to be participating in the process. However, it is also worth recognizing the role that the mononuclear phagocyte series of cells plays in the resolution of inflammation.¹¹⁰ Thus, it is unclear at the present time whether these cells contribute actively to the pathophysiology of asthma and/or are involved in removing and modulating the effects of other cells and the mediators they produce. Because macrophages can manifest many different functional phenotypes, it is entirely possible that the airways of subjects with asthma may contain macrophages that are contributing to the disease as well as cells that are serving to limit the extent of the inflammation and of the pathophysiology.

Platelets

Initial experiments in the rabbit and in the guinea pig suggested that platelet depletion prevented PAF-induced airway responses,^{111,112} although the presence of these cells may not always be necessary.^{113,114} Platelets have been reported in the BAL fluid after allergen challenge,¹¹⁵ and platelet-like structures have been identified histologically in the inflamed airways of guinea pigs.¹¹⁶ Unfortunately, it is not always possible

to identify platelets clearly by morphologic criteria, and specific markers (e.g., MAbs) have not yet been used. However, Jeffery et al.⁸ found that, although platelet numbers (as assessed by electron microscopy) were not increased in subjects with asthma there was aggregation of platelets, together with electron dense fibrous material at the airway luminal edge in biopsy specimens from subjects with symptomatic asthma but not in control subjects. The question of how platelets might cross blood vessel walls and migrate into the tissues has not been addressed. The cells are only poorly phagocytic in vitro and have not yet been demonstrated to have that property in vivo. Alternatively, the platelets might be present as a result of loss of vessel-wall integrity.

In another approach to possible platelet involvement, platelet factor 4 was identified in the plasma of atopic subjects,¹¹⁷ but additional studies have not provided confirmation.¹¹⁸ Platelets do bear the second IgE FcR in a functionally active form, as demonstrated by IgE-dependent oxidative metabolism and cytotoxicity.¹¹⁹ By and large, the evidence that platelets play a pivotal role in human asthma and are directly involved in airway hyperresponsiveness is absent. The observations that suggest a role raise some important questions relating to the possible mechanisms by which platelets might become involved. Intravascular participation of platelets in inflammatory reactions in general, and in airway inflammation in particular, appears highly likely; the cells can release many molecules and mediators that could contribute to the process. If platelets migrate into the tissues themselves, they would certainly represent a potentially important additional inflammatory cell. However, this process needs to be formally demonstrated. In any event, one intriguing role that could be played by this cell is as a major source of lipid mediators.

Lymphocytes

Activated T cells. An area of considerable current interest is the role of the T-lymphocyte in the regulation and expression of the inflammation associated with allergy and asthma. The T cell-derived lymphokines, IL-4, IL-5 and IFN- γ , are intimately involved in the regulation of IgE production.¹²⁰ Some lymphokines are active in the control of EOS production by the bone marrow (IL-5, GM-CSF, and IL-3) and in the regulation of mast cell differentiation. Other lymphokines have chemotactic activity for neutrophils, EOSs, and basophil granulocytes, as well as monocytes, and can activate or degranulate these effector cells. T-lymphocytes also play a general role in the regulation of specific immune responses and

are a possible target cell for desensitization immunotherapy. The cytokine profile of the CD4⁺ helper T cell is diagrammatically represented in Fig. 2.

Direct evidence for T-lymphocyte changes in asthma and allergy come from a variety of sources. Postmortem examination of the airways of patients with asthma revealed large numbers of lymphocytes.^{2,3} Increased numbers of "atypical intraepithelial lymphocytes" were found in an ultrastructural morphologic study of bronchial biopsy specimens obtained during life with subjects with mild asthma.^{9,121} That these lymphocytes are activated is supported by recent analysis of the cellular infiltrate with MABs and immunocytochemical techniques in subjects with atopic asthma with rhinitis and in nonatopic control subjects.⁷ No significant differences were observed between the groups in total leukocyte or total lymphocyte numbers. There were, however, significantly higher numbers of activated (IL-2R⁺) T cells in the group with asthma. Increased natural killer cell activity has been described in the peripheral blood of patients with asthma.¹²² Natural killer cell activity is an inducible property of T cells and of non-T-, and non-B-lymphocytes and is thus a nonspecific indicator of lymphocyte activation.

Corticosteroid-resistant asthma. Measurements in subjects with chronic asthma indicated that patients who were relatively refractory to treatment with corticosteroids had a relative decrease in the numbers of circulating suppressor (CD8) T cells.¹²³ These patients also had an abnormality of T cell growth in vitro (colony counts in soft agar) since, unlike T cells from normal individuals and corticosteroid-responsive subjects, cell proliferation from the refractory patients were not inhibited by optimal concentrations of methyl prednisolone.¹²⁴ A defect in concanavalin A-induced suppressor-cell function has been described in asthma,¹²⁵⁻¹²⁹ and successful immunotherapy was associated with an increase in the relative number of suppressor T cells (OKT8).¹³⁰

Allergen inhalational challenge. T-lymphocyte subset changes have also been studied with the model of bronchial allergen challenge in three separate studies.^{61,131,132} The design of each of these investigations was different, but taking these studies together, it appears that T-lymphocytes bearing the CD4 marker (helper/inducer subset) were depleted in peripheral blood and selectively retained in the lung after challenge, but the kinetics and significance of this finding is as yet unclear. In addition, it appears that there is a difference in the profile of regulatory T cell subsets present in BAL in subjects with asthma who respond

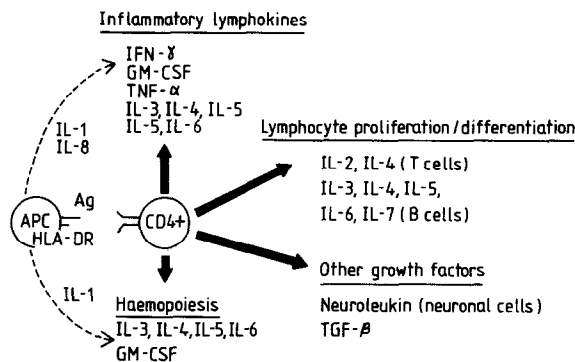


FIG. 2. Cytokines and CD4⁺ ("T helper") cells. Most of our knowledge of T cell-derived cytokines is derived from studies of CD4⁺ T cell lines and clones. In the diagram, Ag is presented in major histocompatibility complex class II (HLA-DR)-restricted fashion by Ag-presenting cells (APC). In asthma, important Ag-presenting cells might include dendritic cells, lung macrophages, endothelial cells, and B cells. The cytokines are grouped according to function; TNF- α , tumor necrosis factor; TS, T suppressor lymphocyte; TGF- β , transforming growth factor.

with an early reaction alone as compared with the dual asthmatic (early and LPR) responders, suggesting that subjects who progress to an LPR to allergen challenge may have a relative inability to recruit CD8⁺ T-lymphocytes to the lung.¹³²

T cells and the LPR. A study of cell traffic and activation in human allergen-induced LPRs in the skin revealed a lymphocyte infiltration that was almost exclusively CD4-positive (helper/inducer subset).¹³³ Some of these T cells were activated in that they stained positively for the presence of IL-2 receptors. Additional evidence of T-lymphocyte activation was provided by the observation that endothelial cells in the allergen-challenged biopsy specimens demonstrated an increased density of HLA-DR expression compared with that of control sites. EOS accumulation and activation were also striking features of the skin LPR with numerous activated EOS (EG2⁺) present at 6 hours after challenge and persisting in tissue for up to 48 hours.

In situ hybridization studies. Two types of murine T cell clones have been defined on the basis of the cytokines they produce.¹³⁴ Th 1 cells express mRNA and secrete IL-2 and IFN- γ , but not IL-4 or IL-5. Th 2 cells produce IL-4 and IL-5, but not IFN- γ or IL-2. Both cell types produce IL-3 and GM-CSF. The genes for IL-3, IL-4, IL-5, and GM-CSF have been cloned and are clustered in the region of the long arm of human chromosome 5 (5q 23-32).¹³⁵ This very close linkage suggests a common evolutionary origin.

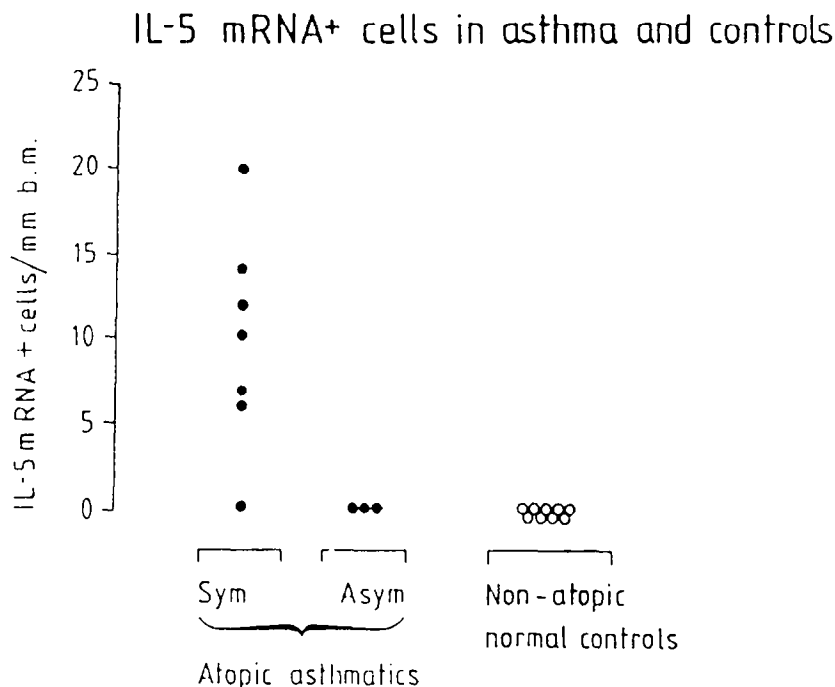


FIG. 3. IL-5 messenger RNA⁺ cells in bronchial mucosal biopsy specimens from atopic subjects with asthma and normal atopic normal control subjects with the technique of in situ hybridization. (Data from Hamid et al.¹⁴⁰)

Wierenga et al.¹³⁶ have demonstrated that in atopic individuals allergen (house dust mite)-specific T cell clones produced a Th 2-like pattern of cytokine production (IL-4, high; IFN- γ , low), whereas nonallergen Ag-specific clones from the same patient produced high IFN- γ and low IL-4. We recently tested the hypothesis that the infiltrating cells associated with allergen-induced LPR have the IL-3, IL-4, IL-5, and GM-CSF gene cluster cytokine profile and, as such, have similarity with murine Th 2-type cells. We used the technique of in situ hybridization on sections from skin biopsy specimens obtained from the sites of allergen-induced LPRs in 14 subjects.¹³⁷

At the allergen-injected sites, most biopsy specimens had positive hybridization signals for IL-3 (8/14), IL-4 (10/14), IL-5 (11/14), and GM-CSF (13/14), whereas only 5/14 were positive for IL-2 mRNA. At the diluent-injected sites, there were a few cells that expressed weak hybridization signals for IL-4 (2/14), IL-5 (1/14), and GM-CSF (3/14). No hybridization was detected for IFN- γ mRNA in biopsy specimens from either the allergen- or diluent-challenged sites. When the allergen-injected site was compared with the diluent-injected control site, there were significant increases in the numbers of cells expressing mRNA for IL-3, IL-4, IL-5, and GM-CSF; the differences for IL-2 and IFN- γ were not significant.

In general, the cytokine mRNA-positive cells were located among the inflammatory infiltrate at the upper part of the dermis. There was no hybridization in the epithelial or connective tissue cells. The specificity of the hybridization signals obtained with the probes was confirmed by the presence of similar intense labeling of cells expressing mRNA for IL-2, IL-3, IL-4, IL-5, and the GM-CSF in a concanavalin-A-stimulated T cell clone from the hyper-IgE syndrome, and IFN- γ mRNA in cytoplasts obtained from lymphoblast cultures 24 hours after PHA stimulation. The absence of hybridization signals with the appropriate sense probes and/or ribonuclease pretreatment provided additional support for the specificity of the hybridization reaction.

We also found significant correlations between IL-5 mRNA-positive cells and IL-3, IL-4, and GM-CSF mRNA-positive cells at the allergen-injected sites; the correlation between IL-5 and IL-2 mRNA⁺ cells was not significant. This supports the possibility of linked transcription of the IL-3, IL-4, IL-5, and GM-CSF gene cluster. There was also evidence of an association between the degree of eosinophilic inflammation and cytokine expression, since there were significantly more EG2⁺ cells in those biopsy specimens that had the highest number of positive signals for IL-5 and IL-4 mRNA. There was a similar trend for IL-3 and GM-CSF, but this was not significant.

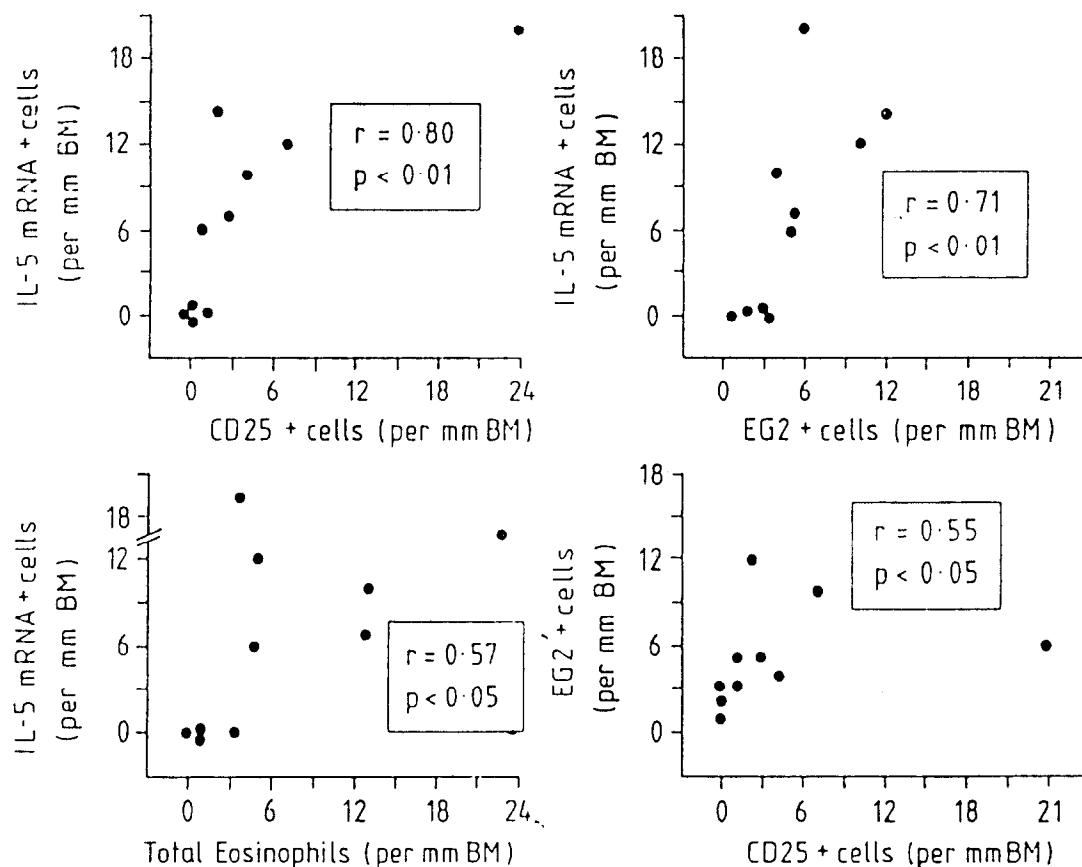


FIG. 4. Correlations between IL-5 mRNA⁺ cells and CD25⁺, EG2⁺, and total EOSs in bronchial mucosal biopsy specimens from atopic subjects with asthma with the technique of in situ hybridization. (Data from Hamid et al.¹⁴⁰).

The detection of mRNA does not necessarily equate with protein synthesis, and it will be necessary to demonstrate that translation and secretion of these lymphokines also occurs. In addition to T-lymphocytes, mast cells also produce lymphokines,¹³⁸ as do macrophages and fibroblasts. Nevertheless, we believe that the cytokine profile observed in the 24-hour LPR provides evidence that, in atopic subjects, allergen induces activation and/or proliferation of cells having the Th 2 pattern. That the antigen itself determines the cloning frequency of murine Th 1 and Th 2 cells was recently stressed by Street et al.¹³⁹

As a follow-up to this study, we also attempted to identify mRNA for IL-5 in biopsy specimens from endobronchial mucosa obtained from subjects with asthma and control subjects.¹⁴⁰ Bronchial biopsy specimens were obtained from 10 subjects with asthma and nine nonatopic, normal control subjects. Specific hybridization signals for IL-5 mRNA were demonstrated within the bronchial mucosa in six of the 10 subjects with asthma (Fig. 3). Cells exhibiting hybridization signals were located beneath the epithelial

basement membrane. In contrast, there was no hybridization in the control group. No hybridization was observed with the sense probe.

The six IL-5 mRNA⁺ subjects with asthma tended to have more severe disease than the mRNA-negative subjects with asthma, as assessed by symptoms and lung function, and demonstrated a significant increase in the degree of infiltration of the bronchial mucosa by secreting (EG2⁺) EOSs and activated (CD25⁺) T-lymphocytes. In the subjects who demonstrated positive IL-5 mRNA, there was a correlation between IL-5 mRNA expression and the number of CD25⁺ and EG2⁺ cells and total EOS count (Fig. 4).

This study provides evidence for cellular localization of IL-5 mRNA in bronchial mucosa of subjects with asthma and supports the concept that this cytokine regulates EOS function in bronchial asthma.

Guinea pig model. The kinetics and phenotype of T-lymphocytes infiltrating the airways of guinea pigs undergoing LARs have also been studied with MABs, cytofluorimetry, and immunocytochemistry.¹⁴¹ Challenge of sensitized animals with aerosolized ovalbu-

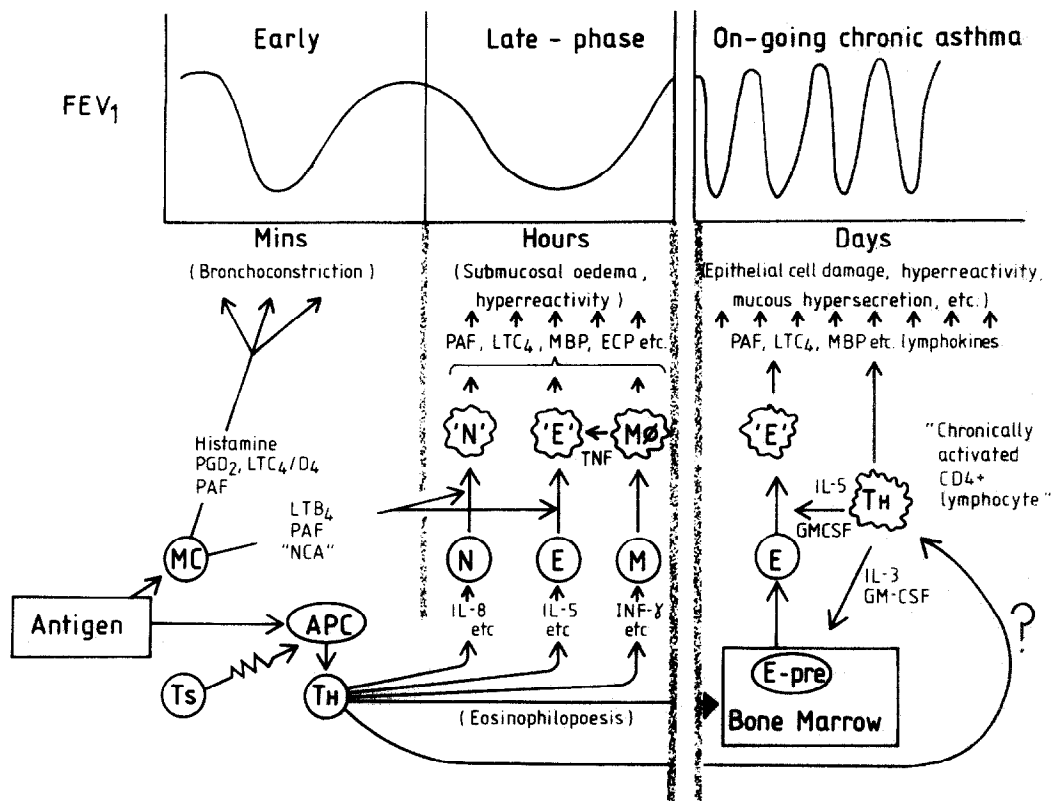


FIG. 5. A scheme to explain the relationship between early, late-phase, and ongoing chronic asthma. The early phase is believed to be dependent on products derived from Fc_R-bearing mediator cells (MC). It is suggested that the LPR is dependent on mast cell-derived chemotactic factors (i.e., LTB₄, PAF, and NCA) as well as products derived from CD4 Th cells. It is speculated that an important feature of ongoing chronic asthma is "chronically activated CD4 lymphocytes" that orchestrate EOS maturation and activation that in turn lead to epithelial cell damage, hyperreactivity, and mucus hypersecretion. (The diagram is greatly simplified; for instance, IL-1 and IL-8 are derived from T cells as well as Ag-presenting cells.)

min was followed by early (2 hour) and late-phase (17 hour) bronchoconstriction. The induction of hypersensitivity by aerosolized Ag was associated with an increase in mucosal T cell numbers, which consisted almost entirely of CD8⁺ T cells. After allergen challenge of fully sensitized animals, a biphasic rise in total T cell (CD3⁺) numbers was observed in the bronchial mucosa, peaking at 17 and 48 hours. A similar pattern of T cell accumulation was observed in the bronchial adventitia but with an extra, early peak at 2 hours. In contrast to the T cell influx of the sensitization phase, the postchallenge infiltrate consisted largely of CD3⁺ CD8⁻ cells. EOS numbers were elevated in both submucosa and adventitia, with a single broad peak between 17 and 48 hours. Although correlations between T cell and EOS numbers varied during the 96 hours of the experiment, strong associations were observed between CD8⁺ numbers and EOSs in the adventitia at 6 hours and between CD3⁺ CD8⁻ numbers and EOSs in the submucosa at 72 hours. No significant changes were detected in

T cell or EOS numbers in the lung parenchyma. There was a postchallenge increase in EOSs (but not T cells) in BAL. In contrast, analysis of blood leukocytes demonstrated no changes in T cell total or subset numbers during the progression of the LAR. These observations indicate that accumulation of T cells in the airways is a feature of the LAR in this model and are consistent with human BAL and skin studies of the allergen-induced LPR. This study also illustrates that evaluation of distant compartments (blood and BAL) may not fully reflect rapidly evolving tissue infiltration in the bronchial mucosa.

ASA (status asthmaticus). Additional evidence to support the view that T cells are involved in the pathogenesis of chronic asthma comes from studies of ASA (status asthmaticus). Corrigan et al.^{1,2} were able to demonstrate significant elevations of the expression of three surface proteins associated with T-lymphocyte activation (IL-2R, class II histocompatibility Ag [HLA-DR], and VLA-1) (Fig. 5) in ASA compared with their expression in control subjects

(subjects with mild asthma and chronic obstructive airway disease and normal individuals). Phenotypic analysis of the IL-2R-positive T-lymphocytes demonstrated that these cells were exclusively of the CD4 "helper-inducer" phenotype. In contrast, CD8 cells were devoid of IL-2R and VLA-1 in both subjects with asthma and control subjects, and the expression of HLA-DR on these cells was not increased above that on cells of control subjects.

The percentages of IL-2R and HLA-DR-positive (but not VLA-1-positive) lymphocytes tended to decrease as the patients were treated and improved clinically. In addition, the serum concentrations of IFN- γ and soluble IL-2R were significantly elevated in patients with ASA as compared with all the control groups.¹⁴³ Concentrations decreased as the patients improved clinically during the first 3-day period of hospital treatment. At 3 days, a significant correlation was observed between the improvement in airway obstruction, as measured by the change in peak expiratory flow rate, and (1) the decrease in percentages of peripheral blood CD4 T-lymphocytes expressing IL-2R and (2) the decrease in the serum concentrations of soluble IL-2R.

Atopic subjects with ASA had significantly smaller numbers of peripheral blood CD4 T cells on admission than nonatopic patients and also tended to have lower or normal serum concentrations of soluble T cell mediators, suggesting that additional factors may have been contributing to the acute bronchoconstriction in these patients. In those patients studied for 7 days, a peak expiratory flow rate of <50% of predicted was associated with significantly higher numbers of activated CD4 T cells and serum concentrations of IL-2R and IFN- γ .

Thus, taken together, these observations provide additional evidence that CD4 T-lymphocyte activation may contribute to the pathogenesis of ongoing, as well as ASA.

Concluding comments

An attempt has been made to review the importance, or otherwise, of various inflammatory cells in the pathogenesis of asthma. The possible participation of neutrophils, EOSs, mast cells, basophils, mononuclear phagocytes, platelets, and lymphocytes have been considered, particularly since products from these cell types have the potential for contributing directly to the features of bronchial asthma. This is diagrammatically represented in Fig. 5. The bronchial epithelium, which has not been considered in this review, is a dynamic tissue that may also play a role in defense as well as damage to the airways. In asthma and in other inflammatory diseases of the airways, there are conspicuous alterations in the epithelium,

many of which may be presumed to result from the inflammatory process itself. In contrast, the epithelium is by no means passive and almost certainly contributes to, and modulates, the inflammation itself.

It is not possible at the present time to judge the importance or otherwise of each individual cell type. It appears far more likely that they act together in a complex cascade. However, in the absence of knowledge of the dynamics of the bronchial pathology associated with the asthma process, anything more than speculation is unwarranted at the present time. Furthermore, the heterogeneity of asthma and associated pathology is still poorly understood; therefore, the likelihood exists that different cells and their mediators may have importance in the various forms of asthma and at different stages in their natural history.

The etiology of asthma remains unknown. One possibility is that, as with allergic asthma in which the inflammation is an inappropriate response to Ag, all asthma is Ag driven. The resident inflammatory cells of the bronchial mucosa, after inappropriate Ag recognition, might become misdirected, forsaking their probable defensive role for one of tissue damage. The nature of the putative activating Ag in nonatopic asthma is unclear. It appears unlikely that asthma can be explained on the basis of atopy in association with common aeroallergens. In contrast, it was of interest that the prevalence of asthma was closely related to the serum IgE level standardized for age and sex.¹⁴⁴ Other etiologic possibilities in asthma include infectious agents, altered (autoimmune) Ags, or a predominantly T cell response to an inhaled aeroallergen independent of the presence of an IgE response. An alternative hypothesis is that epithelial cell loss is the primary defect, exposing the submucosal cells to increased Ag penetration and other inflammatory stimuli.

Nevertheless, there remains a number of particular issues that need to be carefully addressed. These include

1. The elucidation of the factors responsible for the persistence of the inflammation in asthma; this might explain why, in the case of some occupational Ags, the inflammation (and asthma) may continue long after exposure has ceased.
2. The relationship of mucosal inflammation to both bronchial hyperresponsiveness and clinical asthma; this would account for the severe pathologic changes that are sometimes present, even in the absence of clinical disease.
3. The relationship between the immediate and the LPR in provoked asthma (and, in turn, the significance of the LPR to the hyperresponsiveness of persistent asthma).

4. The relevance or otherwise of clinical models of asthma and hyperresponsiveness to the natural disease; the role of bronchial hyperresponsiveness in asthma has been the subject of much debate, and recent observations¹⁴⁵ that individual measurements were not consistently related to concurrent asthma severity suggest that nonspecific bronchial reactivity is only one mechanism underlying air-flow obstruction in asthma.

Therapeutic possibilities are based on clinical and pathologic knowledge and include pharmacologic manipulation of mediators and cytokines and the use of MAbs against cell-surface molecules on various cell types, subsets, or clones. Advances in technology and the ability to probe the airways by methods such as fiberoptic bronchoscopy and mucosal biopsy, together with prospects for analyzing complex biologic fluids in the microenvironment of the bronchial mucosa, may pave the way to a greater understanding of the pathogenesis of asthma.

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