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Inflammatory Mediators of Asthma: An Update

PETER J. BARNES,[a] K. FAN CHUNG, AND CLIVE P. PAGE

Department of Thoracic Medicine (P.J.B., K.F.C), National Heart and Lung Institute, Imperial College, and Department of Pharmacology (C.P.P), Kings College, London, United Kingdom

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[a] Address for correspondence: P. J. Barnes, Department of Thoracic Medicine, National Heart and Lung Institute, Imperial College School of Medicine, Dovehouse St., London SW3 6LY, UK. E-mail: p.j.barnes@ic.ac.uk.

I. Introduction

Asthma is a complex chronic inflammatory disease of the airways that involves the activation of many inflammatory and structural cells, all of which release inflammatory mediators that result in the typical pathophysiological changes of asthma (Barnes, 1996a) (table 1). By inflammatory mediators, we mean cell products that are secreted and exert functional effects. We reviewed the mediators of asthma in 1988 (Barnes *et al.,* 1988), but since then there have been major advances in our understanding of the mechanisms of asthma and the role of inflammatory mediators. There is now greater understanding of each mediator; in addition, novel mediators of asthma, such as the cytokines, have been identified. To date, >50 different mediators have been identified in asthma. Advances in this field have been greatly assisted by the development of potent and specific inhibitors that either block the inflammatory mediator receptors or inhibit mediator synthesis.

In writing this review, we have focused on new developments since 1988 and have emphasized studies in humans wherever possible. There is a vast and rapidly increasing body of literature on mediators of asthma; therefore, we have been forced to be somewhat selective. We have chosen to emphasize the mediators and effects that we think are most relevant to human asthma.

A. Cellular Origin of Mediators

Many inflammatory cells are recruited to asthmatic airways or are activated in situ. These include mast cells, macrophages, eosinophils, T lymphocytes, dendritic cells, basophils, neutrophils, and platelets. It is now increasingly recognized that structural cells may also be important sources of mediators in asthma. Airway epithelial cells, smooth muscle cells, endothelial cells, and fibroblasts are all capable of synthesizing and releasing inflammatory mediators (Levine, 1995; Saunders *et al.,* 1997; John *et al.,* 1997). Indeed, these cells

TABLE 1
Effects of inflammatory mediators implicated in asthma

Mediator	Broncho-constriction	Airway secretion	Plasma exudation	Neural effects	Chemotaxis	AHR[a]
Histamine	++	+	+	+	+	−
Serotonin	−	?	+	+	−	−
Adenosine	(+)	?	(+)	+	±	−
PGD_2 and $PGF_{2\alpha}$	++	+	?	+	?	+
PGE_2	−	+	−	+	+	−
Tx	++	?	+	+	±	+
LTB_4	−	−	±	−	+++	±
LTC_4, LTD_4 and LTE_4	+++	++	++	±	+	±
PAF	++	+	++	+	+++	++
Bradykinin	+	+	++		−	−
SP	++	++	++	+++	±	−
NKA	++	+	+		−	−
CGRP	±	+	(+)	?	+	−
ET	+++	+	+	+	?	?
Complement fragments	+	+	+	?	++	−
ROS	(+)	+	+	−	?	−
NO	−	+	(+)	+	+	−
Tryptase	(+)	++	+	−	+	+

[a] AHR, airway hyperresponsiveness; −, no effect; ±, possible effect; +, small effect; ++, moderate effect; +++, strong effect; ?, uncertain or undetermined effect; parentheses indicate indirect effects.

may become the major sources of inflammatory mediators in the airway, and this may explain how asthmatic inflammation persists even in the absence of activating stimuli.

B. Synthesis and Metabolism

There have been major advances in our understanding of the synthetic pathways involved in the synthesis of inflammatory mediators. Many of the key enzymes have now been cloned; in several cases, specific inhibitors have been developed that may have useful therapeutic effects. 5-Lipoxygenase (5-LO)[b] inhibitors, which inhibit the synthesis of leukotrienes (LTs), have already been shown to have beneficial effects in the control of clinical asthma and are now available for clinical use (Israel *et al.,* 1996).

C. Mediator Receptors

Many inflammatory mediator receptors have now been cloned. The receptor for platelet-activating factor (PAF) was the first inflammatory mediator receptor to be cloned (Honda *et al.,* 1991), and many inflammatory mediator receptors have been sequenced since then. The receptors for many inflammatory mediators have the typical seven-transmembrane domain structure that is expected for G protein-coupled receptors. However, receptors for cytokines and growth factors have markedly different structures, and usually two or more subunits are involved (Kishimoto *et al.,* 1994). Receptor cloning has yielded a much better understanding of receptor function, because the receptors can be expressed in cell lines, allowing investigation of the "pure" pharmacological features of the receptor and enabling screening for drugs that interact with the receptor. This has been important in elucidating the signal transduction pathways involved in receptor function. Many signal transduction pathways have now been identified. For noncytokine mediators, inflammatory receptors are often coupled, through G proteins (G_q and G_i), to phosphoinositide (PI) hydrolysis, but it is increasingly recognized that other pathways may also be activated, including the complex mitogen-activated protein (MAP) kinase pathways that are involved in more long term effects of

[b] Abbreviations: ACE, angiotensin-converting enzyme; AMP, adenosine monophosphate; AP-1, activator protein-1; bFGF, basic fibroblast growth factor; $[Ca^{2+}]_i$, intracellular calcium ion concentration; CCR, CC chemokine receptor; cDNA, complementary deoxyribonucleic acid; CGRP, calcitonin gene-related peptide; cNOS, constitutive nitric oxide synthase; COX, cyclooxygenase; cys-LT, cysteinyl-leukotriene; ECE, endothelin-converting enzyme; EGF, epidermal growth factor; eNOS, endothelial nitric oxide synthase; ET, endothelin; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GMP, guanosine monophosphate; GRO, growth-related oncogene protein; HETE, hydroeicosatetraenoic acid; HMT, histamine N-methyltransferase; HMW, high molecular weight; HPETE, hydroperoxyeicosatetraenoic acid; 5-HT, 5-hydroxytryptamine; ICAM, intercellular adhesion molecule; IFN, interferon; Ig, immunoglobulin; IGF, insulin-like growth factor; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; i-NANC, inhibitory nonadrenergic noncholinergic; iNOS, inducible nitric oxide synthase; IP_3, inositol-1,4,5-trisphosphate; LMW, low molecular weight; LO, lipoxygenase; LT, leukotriene; LX, lipoxin; MAP, mitogen-activated protein; MCP, macrophage chemotactic peptide; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; mRNA, messenger ribonucleic acid; L-NAME, N^G-L-arginine methyl ester; NANC, nonadrenergic noncholinergic; NEP, neutral endopeptidase; NF-κB, nuclear factor-κB; NF-AT, nuclear factor of activated T cells; NK, neurokinin; L-NMMA, N^G-monomethyl-L-arginine; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; PAF, platelet-activating factor; PAGPC, 1-palmitoyl-2-acetoyl-sn-glyceryl-3-phosphocholine; PDGF, platelet-derived growth factor; PG, prostaglandin; PI, phosphoinositide hydrolysis; PKC, protein kinase C; PPT, preprotachykinin; RANTES, regulated on activation, normal T cell-expressed, and secreted protein; ROS, reactive oxygen species; SCF, stem cell factor; SOD, superoxide dismutase; SP, substance P; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor; TRAF, tumor necrosis factor receptor-associated factor; Tx, thromboxane; VCAM, vascular cell adhesion molecule; VIP, vasoactive intestinal polypeptide.

mediators. Cytokine receptors signal through complex pathways, including MAP kinases and other protein kinases, that result in the activation of transcription factors. Transcription factors regulate the expression of many genes, including inflammatory genes themselves.

The cloning of receptors has made it possible to study the factors regulating their expression. This may be of particular relevance in asthma, because the inflammatory state may alter the gene expression, translation, or function of receptors, thus affecting responsiveness to different mediators.

D. Mediator Effects

Inflammatory mediators produce many effects in the airways, including bronchoconstriction, plasma exudation, mucus secretion, neural effects, and attraction and activation of inflammatory cells. Although the acute effects of mediators have been emphasized, there is increasing recognition that mediators may result in long-lasting structural changes in the airways that are also mediated by the release of inflammatory mediators. These changes may include fibrosis resulting from the deposition of collagen, which is seen predominantly under the epithelium even in patients with mild asthma. The airway smooth muscle layer is also thickened in asthma, and this is likely the result of increases in the number of smooth muscle cells (hyperplasia) and increases in their size (hypertrophy) (Knox, 1994). There may be proliferation of airway vessels (angiogenesis) (Kuwano *et al.,* 1993) and of mucus-secreting cells. There may also be changes in the innervation of the airways.

E. Involvement of Mediators in Asthma

There are several lines of evidence that may implicate a mediator in asthma. Firstly, it may mimic features of clinical asthma. Secondly, the mediator may be produced in asthmatic patients. Thus, mediators or their metabolites may be detected in plasma (e.g., histamine), urine (e.g., LTE_4), or, more likely, the airways (in biopsies, bronchoalveolar lavage fluid, induced sputum, or exhaled air). However, this does not necessarily mean that the mediator plays any important role in asthma. The best evidence for the involvement of a mediator in asthma is obtained with the use of specific blockers. These may be drugs that block the synthesis of the mediators (e.g., 5-LO inhibitors) or drugs that block their receptors (e.g., antihistamines). Use of new and selective mediator blockers has enormously increased our understanding of the individual mediators and also of asthma itself. Although it is unlikely that blockade of a single mediator will be entirely effective in controlling asthma, there is accumulating evidence that some mediators are more important than others. PAF receptor antagonists are of no obvious clinical benefit in asthma (Kuitert *et al.,* 1993), but cysteinyl-LT (cys-LT) receptor antagonists have considerable clinical effects (O'Byrne *et al.,* 1997).

The role of a mediator in asthma may be difficult to assess when the mediator has a long term effect on airway function. It is easy to measure the effect of a mediator on airway smooth muscle, but it is more difficult to determine its effect on airway microvascular leakage and mucus secretion. It may be even more difficult to determine the role of a mediator on chronic inflammatory effects, such as airway smooth muscle proliferation and fibrosis, that may develop over many years. However, prevention of the long term consequences of asthmatic inflammation, such as irreversible airway narrowing, may be an important goal of asthma therapy, and it is necessary to devise methods to investigate how mediators may affect these long term consequences of asthma.

Asthma has a characteristic clinical pattern, and the histological appearance of asthma is very similar among patients, even when there are differences in asthma severity or in whether or not the asthma is allergic. However, it is likely that there are differing mechanisms of asthma among patients and that different patterns of inflammatory mediators are involved. This suggests that mediator antagonists would have different effects in different patients. This has already been observed in the use of anti-LTs, because some patients appear to have much better therapeutic responses than others. This might be related to polymorphisms of the 5-LO gene (In *et al.,* 1997), but there might be differences that relate to the type of asthma. Patients with aspirin-sensitive asthma are particularly helped by anti-LTs, consistent with a critical role for cys-LTs in this type of asthma. As more mediator antagonists become available, other patients who respond well to a particular antagonist may be identified and the heterogeneity of asthma may be revealed.

F. Chronic Inflammation

Although in the past much attention has been paid to acute inflammatory responses (such as bronchoconstriction, plasma exudation, and mucus hypersecretion) in asthma, it is being increasingly recognized that chronic inflammation is an important aspect of asthma (Redington and Howarth, 1997). This chronic inflammation may result in structural changes in the airway, such as fibrosis (particularly under the epithelium), increased thickness of the airway smooth muscle layer (hyperplasia and hypertrophy), hyperplasia of mucus-secreting cells, and new vessel formation (angiogenesis). Some of these changes may be irreversible, leading to fixed narrowing of the airways. These chronic inflammatory changes are mediated by the secretion of distinct mediators, although their role in asthma is still far from certain. These factors include cytokines and growth factors. Cytokines are a large group of protein mediators that play a critical role in determining the nature of the inflam-

matory response and its persistence. They play a key role in the pathophysiological changes in chronic asthma and are being increasingly recognized as important targets for treatment (Robinson *et al.,* 1993c; Barnes, 1994a; Drazen *et al.,* 1996).

G. Transcription Factors

Transcription factors are DNA-binding proteins that regulate the expression of inflammatory genes, including enzymes involved in the synthesis of inflammatory mediators and protein and peptide mediators. Transcription factors therefore play a critical role in the expression of inflammatory proteins in asthma, because many of these proteins are regulated at a transcriptional level (Barnes and Karin, 1997; Barnes and Adcock, 1998). These transcription factors include nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), which are universal transcription factors that are involved in the expression of multiple inflammatory and immune genes and may play a key role in amplifying the inflammatory response. Other transcription factors, such as nuclear factor of activated T cells (NF-AT), are more specific and regulate the expression of a restricted set of genes in particular types of cell; NF-AT regulates the expression of interleukin (IL)-2 and IL-5 in T lymphocytes.

H. Mediator Interactions

Many mediators are released in asthma, and it is clear that these mediators interact with each other in some way. Mediators may act synergistically to enhance each other's effects, or one mediator may modify the release or action of another mediator. Little is currently understood regarding these mediator interactions, however. The development of mediator antagonists will greatly facilitate elucidation of such interactions.

II. Amine Mediators

A. Histamine

Histamine [2-(4-imidazole)ethylamine] was the first mediator implicated in the pathophysiological changes of asthma, when it was found to mimic several features of the disease. Although histamine has been studied extensively as a mediator of asthma, there are several new findings regarding the role of this mediator in asthma.

1. Synthesis and metabolism. Histamine is synthesized and released by mast cells in the airway wall and by circulating and infiltrating basophils. Although airway mast cells are likely to be the major cellular source of histamine in asthma, there is increasing evidence that basophils may be recruited to asthmatic airways and may release histamine in response to cytokine histamine-releasing factors (Schroeder and MacGlashan, 1997).

Histamine is formed by decarboxylation of the amino acid histidine by the enzyme L-histidine decarboxylase (EC 4.1.1.22), which is dependent on the cofactor pyridoxal-5′-phosphate. Histamine is stored in granules within mast cells and basophils, where it is closely associated with the anionic proteoglycans heparin (in mast cells) and chondroitin-4-sulfate (in basophils). Histamine may be released when these cells degranulate in response to various immunological [immunoglobulin (Ig)E or cytokines] or nonimmunological (compound 48/80, calcium ionophore, mastoparin, substance P (SP), opioids, or hypo-osmolar solutions) stimuli.

Only a small amount of the histamine released (2 to 3%) is excreted unchanged. The remainder is metabolized, via two major pathways, and excreted in the urine. The majority (50 to 80%) is metabolized by histamine N-methyltransferase (HMT) (EC 2.1.1.8) to N-methylhistamine, which is itself metabolized by monoamine oxidase to N-methylimidazole acetic acid, the major urinary metabolite. The remaining histamine is metabolized by diamine oxidase (EC 1.4.3.6) to imidazole acetic acid, which is excreted in the urine. HMT appears to be the most important enzyme contributing to the degradation of histamine in the airways, because blockers of HMT (such as SKF 91488) increase the bronchoconstricting action of histamine in vitro and in vivo, whereas diamine oxidase inhibition is without effect (Sekizawa *et al.,* 1993). HMT is expressed in airway epithelial cells and may therefore be responsible for the local metabolism of histamine released from airway mast cells. Mechanical removal of airway epithelium enhances the bronchoconstriction response to histamine in vitro (Barnes *et al.,* 1985; Flavahan *et al.,* 1985; Knight *et al.,* 1990); this might be the result, in part, of loss of the metabolizing enzyme. Furthermore, experimental viral infections result in reduced epithelial HMT activity in association with increased responsiveness to inhaled histamine (Nakazawa *et al.,* 1994).

2. Receptors. Histamine has multiple effects on airway function that are mediated by specific surface receptors on target cells (Barnes, 1991). Three types of histamine receptors have now been recognized pharmacologically (Hill, 1990). Histamine receptors were first differentiated into H_1 and H_2 receptors by Ash and Schild in 1966, when it was found that some responses to histamine were blocked by low doses of mepyramine (pyrilamine), whereas others were insensitive. This classification was supported by the development of H_2 receptor-selective antagonists, such as cimetidine and ranitidine. Both H_1 and H_2 receptors have been cloned. Both have the seven-transmembrane domain motif typical of G protein-coupled receptors. A third histamine receptor subtype, termed H_3, has been described more recently; this receptor acts as an inhibitory autoreceptor in the central nervous system (Schultz *et al.,* 1991).

a. H_1 RECEPTORS. H_1 receptors have been cloned from cows (Yamashita *et al.,* 1991), rats (Fujimoto *et al.,* 1993), guinea pigs (Horio *et al.,* 1993), and humans (De Backer *et al.,* 1993; Fukui *et al.,* 1994). The published

sequences suggest that there are surprisingly large differences among species, consistent with the sometimes marked differences in the responses to histamine among species, with lower activities in rats and mice, compared with guinea pigs and humans (Hill, 1990). H_1 receptors mediate most of the effects of histamine that are relevant to asthma. H_1 receptors have been demonstrated in animal and human lung by direct receptor binding techniques (Carswell and Nahorski, 1982; Casale *et al.,* 1985). [^{3}H]Mepyramine binding to human lung homogenates is complex, with at least three sites with different affinities (Casale *et al.,* 1985). There have been no autoradiographic mapping studies, because of the unsuitability of currently available radioligands. Antigen-induced, IgE-dependent anaphylaxis in chopped human lung causes increases in both cyclic adenosine monophosphate (AMP) and cyclic guanosine monophosphate (GMP) levels. The rise in cyclic GMP levels is blocked by an H_1 receptor antagonist, suggesting that this response is linked to H_1 receptor activation (Platshon and Kaliner, 1978). The effect of histamine on cyclic GMP levels in guinea pig lung is dependent on L-arginine, suggesting that H_1 receptor stimulation increases the release of nitric oxide (NO), which subsequently increases cyclic GMP levels by activating soluble guanylyl cyclase (Leurs *et al.,* 1991). The bronchoconstricting effect of histamine is enhanced by NO synthase (NOS) inhibitors, suggesting that the release of NO stimulated by histamine partially counteracts the direct bronchoconstricting action of airway smooth muscle H_1 receptors (Nijkamp *et al.,* 1993). This may not occur in human airways, because there is no increase in the bronchoconstriction response to histamine after inhalation of NOS inhibitors (Yates *et al.,* 1995) and no increase in the levels of exhaled NO (Kharitonov *et al.,* 1995).

Northern analysis has demonstrated that there is a high level of expression of H_1 receptor messenger ribonucleic acid (mRNA) in lung (Yamashita *et al.,* 1991; Horio *et al.,* 1993; Fujimoto *et al.,* 1993; De Backer *et al.,* 1993; Fukui *et al.,* 1994). H_1 receptor mRNA is strongly expressed in bovine tracheal smooth muscle, and mRNA expression is inhibited by protein kinase C (PKC) activation (Pype *et al.,* 1998). Because histamine stimulates PKC via PI hydrolysis through H_1 receptor activation, this might be a mechanism of down-regulation of H_1 receptors. However, exposure of bovine tracheal smooth muscle to histamine is not associated with any effect on H_1 receptor mRNA levels, and regulation appears to be the result of phosphorylation of the receptor by an unidentified G protein-related kinase (Pype *et al.,* 1998).

H_1 receptors are coupled to PI turnover, with release of intracellular calcium ions. Thus, transfected H_1 receptors are coupled to a rise in the intracellular calcium ion concentration ($[Ca^{2+}]_i$) (Irfdale *et al.,* 1993). In airway smooth muscle cells, the contractile response to histamine is partly reduced by removal of extracellular Ca^{2+} and by treatment with calcium channel blockers (Cheng and Townley, 1983; Drazen *et al.,* 1983). This suggests that the bronchoconstriction response to histamine is partly mediated by opening of voltage-dependent calcium channels. However, most of the contractile response is unaffected by extracellular Ca^{2+}. Histamine stimulates a transient elevation of $[Ca^{2+}]_i$ (measured as fura-2 fluorescence in cultured canine tracheal smooth muscle cells) that is largely independent of extracellular Ca^{2+} (Kotlikoff *et al.,* 1987; Kotlikoff, 1988; Takuwa *et al.,* 1988).

b. H_2 RECEPTORS. H_2 receptors have been cloned from dogs (Gantz *et al.,* 1991b) and humans (Gantz *et al.,* 1991a). Although H_2 receptors are present in the airways, their clinical relevance is unclear, because H_2 receptor antagonists have few measurable effects on airway function. H_2 receptors have been detected in lung using [^{3}H]tiotidine, although their cellular localization has not yet been reported (Foreman *et al.,* 1985). Histamine stimulates an increase in cyclic AMP levels in lung fragments that is blocked by H_2 receptor antagonists, indicating that H_2 receptors are positively coupled to adenylyl cyclase in lung (Platshon and Kaliner, 1978).

c. H_3 RECEPTORS. Although H_3 receptors have also been identified in lung by binding studies (Arrang *et al.,* 1987), functional studies are limited. The H_3 receptor has not yet been cloned.

3. Effects on airways.

a. AIRWAY SMOOTH MUSCLE. Histamine stimulates PI hydrolysis in airway smooth muscle (Grandordy and Barnes, 1987; Hall and Hill, 1988; Daykin *et al.,* 1993), and there is a close association of receptor occupancy, PI hydrolysis, and the contractile response, indicating that there are few or no "spare" receptors (Grandordy and Barnes, 1987). Histamine also increases the concentration of inositol-1,4,5-trisphosphate (IP_3) in airway smooth muscle, although the magnitude of the increase is less than with cholinergic agonists, which may reflect lower receptor density (Chilvers *et al.,* 1989). In cultured human airway smooth muscle cells, histamine increases $[Ca^{2+}]_i$ via an increase in IP_3 levels (Hardy *et al.,* 1996).

Bronchoconstriction was one of the first recognized effects of histamine. Inhaled or intravenously administered histamine causes bronchoconstriction, which is inhibited by H_1 receptor antagonists (such as chlorpheniramine, terfenadine, or astemizole). Histamine contracts both central and peripheral airways in vitro, with a more potent effect on peripheral airways. Asthmatic patients are more sensitive to the bronchoconstricting effects of inhaled and intravenously administered histamine than are normal individuals; this is a manifestation of airway hyperresponsiveness. However, there is little evidence for increased contractile responsiveness to histamine in asthmatic airways in vitro (Whicker *et al.,* 1988), suggesting that the hyperresponsiveness to histamine in asthma is not the result of any change in histamine receptors in airway smooth muscle. In human airway smooth muscle in vitro, there is a

certain degree of basal tone. This is reduced by H_1 receptor antagonists, suggesting that basal release of histamine (presumably derived from mast cells) contributes to this tone (Ellis and Undem, 1994). This is consistent with the bronchodilating effects reported for intravenously administered chlorpheniramine and orally administered terfenadine in asthmatic patients but not in normal individuals (Eiser *et al.,* 1981; Cookson, 1987).

Histamine also induces proliferation of cultured airway smooth muscle, and this is associated with increased expression of c-*fos* (Panettieri *et al.,* 1990). It is not certain whether this effect of histamine is mediated by the H_1 receptor but this is likely, because H_1 receptor stimulation may activate PKC and thereby c-*fos* expression.

H_2 receptors that mediate bronchodilation have been identified in some species, including cats, rats, rabbits, sheep, and horses (Chand and Eyre, 1975). In some species, such as rabbits, the H_2 receptor-mediated response predominates, because histamine itself is a bronchodilator. Histamine increases cyclic AMP content in guinea pig tracheal smooth muscle cells, and this is blocked by an H_2 receptor antagonist (Florio *et al.,* 1992). Interestingly, dexamethasone enhances this response to histamine, without affecting the affinity or binding of H_2 receptors. Human peripheral lung strips show a relaxation response to histamine via H_2 receptors (Vincenc *et al.,* 1984), although this is more likely to reflect a relaxation effect on pulmonary vessels, rather than peripheral airways. H_2-selective blockers, such as cimetidine and ranitidine, do not cause bronchoconstriction in normal or asthmatic individuals and do not increase the bronchoconstriction response to inhaled histamine (Nogrady and Bevan, 1981; Thomson and Kerr, 1980; Braude *et al.,* 1994). Similarly, the H_2 receptor agonist impromidine has no effect on normal or asthmatic airways (White *et al.,* 1987).

A defect in H_2 receptor-mediated bronchodilation has been reported in sheep with allergic airway inflammation (Ahmed *et al.,* 1983), and there is evidence that H_2 receptor-mediated gastric secretion may be impaired in patients with asthma (Gonzalez and Ahmed, 1986). This has suggested that there may be a defect in H_2 receptor function in asthmatic airways (Chand, 1980), although there is no direct evidence that this is the case.

Histamine-induced bronchoconstriction shows desensitization in some species, such as guinea pigs. This appears to be the result of release of prostaglandin (PG)E_2 and is blocked by indomethacin (Orehek *et al.,* 1975; Haye-Legrand *et al.,* 1986). Similar desensitization to inhaled histamine has been reported in normal subjects and in patients with mild asthma (Manning and O'Byrne, 1988). This loss of effect is blocked by indomethacin and appears to be mediated by H_2 receptors (Jackson *et al.,* 1981). Histamine desensitization in human airways in vitro is mediated by H_2 receptors and is blocked by indomethacin treatment and by epithelium removal (Knight *et al.,* 1992). This may contribute to the enhanced bronchoconstricting effect of histamine in vitro after epithelium removal (Knight *et al.,* 1990). Histamine may activate H_2 receptors on epithelial cells to release PGE_2, thus counteracting the bronchoconstricting action of histamine on airway smooth muscle (mediated by H_1 receptors).

The H_3 receptor agonist (*R*)-α-methylhistamine has no effect on airway smooth muscle tone in vitro or in vivo (Ichinose *et al.,* 1989; Ichinose and Barnes, 1989a,b), and the H_3 receptor antagonist thioperamide does not influence either basal activity or the bronchoconstriction response to histamine, suggesting that H_3 receptors are not functionally expressed in airway smooth muscle. Furthermore, inhaled (*R*)-α-methylhistamine has no effect on airway function in asthmatic patients (O'Connor *et al.,* 1993).

b. VESSELS. In human skin, histamine causes a vasodilating response (flare) that is mediated by H_1 receptors. Human bronchial vessels are relaxed by low concentrations of histamine in vitro but are constricted by high concentrations (Liu *et al.,* 1990). Both effects are blocked by mepyramine, indicating that H_1 receptors are involved. It is likely that the vasodilating response is the result of the release of NO from endothelial cells and that the vasoconstricting effect is the result of the direct action of histamine on vascular smooth muscle H_1 receptors. Histamine appears to increase airway blood flow in vivo, but there are doubts regarding whether this is mediated by H_1 or H_2 receptors because, even in the same species, different effects of H_1 and H_2 blockers have been reported (Long *et al.,* 1985; Webber *et al.,* 1988).

Histamine also causes plasma extravasation from postcapillary venules in the bronchial circulation, and this effect is blocked by H_1 receptor antagonists. Measurement of plasma exudation in human airways is difficult, but it is likely that histamine induces plasma exudation, as in rodent airways. In support of this is the finding that histamine, when injected intradermally, causes a wheal that is blocked by H_1 but not H_2 antagonists (Summers *et al.,* 1981). Whether histamine contributes to the plasma exudation seen after allergen challenge in humans has not been determined, but in guinea pigs antihistamines had marked inhibitory effects on allergen-induced plasma extravasation in proximal airways, whereas a LT inhibitor had a greater effect in more peripheral airways (Evans *et al.,* 1989). Although histamine causes plasma extravasation in the airways, this makes relatively little contribution to the airway narrowing induced by histamine (Tokuyama *et al.,* 1991).

Although vasodilating H_2 receptors have been clearly demonstrated in human pulmonary vessels (Barnes and Liu, 1995), their role in the bronchial circulation is less well defined, and there appear to be species differences. In sheep and dogs, histamine induces an increase in bronchial blood flow that is mediated by H_2 receptors

(Long *et al.,* 1985; Parsons *et al.,* 1992b). In human bronchial vessels in vitro, the vasodilating action of histamine is not blocked by H_2 antagonists (Liu *et al.,* 1990). Lung permeability (measured by the clearance of ^{99m}Tc-labeled diethylenetriaminepentaacetate) is increased by inhaled histamine, and this is blocked by the H_2 receptor antagonist ranitidine but not by the H_1 receptor antagonist terfenadine (Braude *et al.,* 1994). It is uncertain whether diethylenetriaminepentaacetate clearance measures alveolar or airway permeability or pulmonary blood flow.

c. SECRETIONS. Histamine stimulates the secretion of mucus glycoproteins in human airways in vitro, but this is not blocked by H_1 antagonists and the H_1 agonists 2-methylhistamine and 2-pyridylethylamine are without effect (Shelhamer *et al.,* 1980). It is difficult to study the production of mucus from the lower respiratory tract in humans in vivo, but studies have been performed on the more accessible nasal secretions. Histamine induces a rise in secretory IgA and lactoferrin, which implies active glandular secretion, and this is blocked by chlorpheniramine, suggesting that H_1 receptors are involved (Raphael *et al.,* 1989).

Histamine also increases chloride ion transport in canine tracheal epithelial cells, and this response is blocked by H_1 antagonists (Marin *et al.,* 1977). In a bronchial epithelial cell line (BEAS-2B), histamine increases $[Ca^{2+}]_i$ and releases a variety of mediators, including interleukin (IL)-6 and fibronectin, but not lipid mediators (Noah *et al.,* 1991). These effects are probably mediated by H_1 receptors. Histamine also increases the expression of intercellular adhesion molecule-1 (ICAM-1) and the surface marker HLA-DR in primary cultured human bronchial epithelial cells (Vignola *et al.,* 1993). This effect is largely mediated by H_1 receptors, but H_2 antagonists at high concentrations also have an inhibitory effect. Interestingly, cycloheximide blocked these effects of histamine, suggesting that histamine induced the synthesis of a protein critical to these responses.

The increase in mucus glycoprotein secretion in human airways in vitro in response to histamine is blocked by cimetidine and mimicked by the H_2 agonist dimaprit, confirming that H_2 receptors are involved in this response (Shelhamer *et al.,* 1980). However, the effect of histamine is very weak, compared with that of other secretagogues such as muscarinic agonists, suggesting that this effect of histamine is unlikely to be of major importance. Histamine is reported to directly activate rodent airway goblet cells via H_2 receptors, but whether this is the case in human airways is not yet known (Tamaoki *et al.,* 1997).

d. NERVES. In many species, the bronchoconstricting effect of histamine is partially mediated by a vagal cholinergic reflex and may be modulated by muscarinic receptor antagonists. In dogs, histamine increases the discharge of "irritant" receptors in vivo (Aδ-fibers), and these effects are abolished by H_1 antagonists. However, in vitro measurements of single afferent fibers in guinea pig trachea show no evidence for activation of either Aδ- or C-fibers by histamine (Fox *et al.,* 1993). This suggests that the in vivo effect of histamine on airway sensory nerves may be secondary to some other effect, such as bronchoconstriction. In guinea pig lung, histamine appears to release neuropeptides, such as SP and calcitonin gene-related peptide (CGRP), from capsaicin-sensitive sensory nerves via H_1 receptors (Saria *et al.,* 1988).

Histamine also augments vagus nerve-induced bronchoconstriction in dogs, without increasing the response to acetylcholine (Loring *et al.,* 1978; Kikuchi *et al.,* 1984). The effect of histamine on cholinergic nerves is mediated, in part, by stimulation of acetylcholine release from postganglionic nerve terminals, because the enhancing effect of histamine in dogs is seen even after vagus nerve sectioning, which abolishes all reflex effects (Shore *et al.,* 1983). This suggests that histamine acts on prejunctional H_1 receptors to enhance acetylcholine release (Barnes, 1992a). In guinea pigs, there is evidence for direct activation of parasympathetic neurons by histamine, acting via H_1 receptors (Myers and Undem, 1995). The role of cholinergic reflexes in the bronchoconstriction response to histamine in human airways is less certain. A significant reduction of the bronchoconstriction response to histamine after anticholinergic drug treatment was reported in some studies (Eiser and Guz, 1982), whereas others found no effect (Casterline *et al.,* 1976). This may be related to the dose of histamine administered, because anticholinergic agents may block the bronchoconstricting effect of small, but not large, doses of inhaled histamine.

(*R*)-α-Methylhistamine has an inhibitory effect on vagus nerve-induced contraction of an innervated guinea pig tracheal tube preparation but has no effect on acetylcholine-induced contraction, indicating that it may modulate cholinergic neurotransmission (Ichinose *et al.,* 1989). The inhibitory effect is greater for vagus nerve stimulation (preganglionic) than for electrical field stimulation (postganglionic), indicating that modulation occurs both at parasympathetic ganglia and at postganglionic nerve endings (Ichinose *et al.,* 1989). These effects are blocked by thioperamide but not by mepyramine or cimetidine, indicating that H_3 receptors are involved and presumably localized to parasympathetic ganglionic neurons and postganglionic cholinergic nerve terminals. Histamine, in the presence of H_1 and H_2 receptor antagonists, has similar inhibitory actions and has no effect at low concentrations. In human bronchi in vitro, an inhibitory effect of (*R*)-α-methylhistamine on electrical field stimulation-induced contraction, but not acetylcholine-induced contraction, is seen, indicating a similar inhibitory effect on postganglionic cholinergic nerves, which is inhibited by thioperamide (Ichinose and Barnes, 1989a). This demonstrates the presence of H_3 receptors on cholinergic nerves in human airways.

Histamine may also exert prejunctional effects on the release of neuropeptides from airway sensory nerves, via H_3 receptors. (*R*)-α-Methylhistamine has an inhibitory effect on vagus nerve-induced bronchoconstriction in guinea pig airways but has no effect on the equivalent degree of bronchoconstriction induced by tachykinins, indicating a modulatory effect on the release of tachykinins from sensory nerves. This effect is blocked by thioperamide, indicating that H_3 receptors are involved (Ichinose and Barnes, 1989b). Similarly, (*R*)-α-methylhistamine inhibits vagus nerve-induced plasma extravasation, without affecting leakage induced by SP, indicating a modulatory effect of H_3 receptors on neurogenic inflammation (Ichinose *et al.,* 1990b). The functional relevance of the inhibition of H_3 receptors on airway nerves may be that this acts as a protective inhibitory feedback mechanism (Barnes and Ichinose, 1989). There is a close relationship between airway mast cells and nerves. If mast cells exhibit a basal release of histamine in asthma, the low concentrations of histamine may act on H_3 receptors on cholinergic nerve terminals and ganglia to inhibit neurotransmission and thus prevent activation of bronchoconstricting reflexes. Similarly, histamine inhibits the release of neuropeptides from sensory nerves in airways and thus prevent neurogenic leak. When mast cells are degranulated by allergen, there is a massive release of histamine, which overwhelms the H_3 receptor system and predominantly activates H_1 receptors on airway smooth muscle and endothelial cells.

e. INFLAMMATORY CELLS. Histamine may also have effects on inflammatory cells, and it has been found to influence the release of cytokines and inflammatory mediators from a variety of inflammatory and immune cells (Falvs and Merety, 1992). The relevance of this is uncertain, because H_1 antagonists do not appear to have significant anti-inflammatory effects. Histamine is a selective chemoattractant for eosinophils (Clark *et al.,* 1975) and activates human eosinophils, as reflected by a rise in $[Ca^{2+}]_i$ (Raible *et al.,* 1992). The nature of the receptor on eosinophils is not clear; the receptor does not fit into the $H_1/H_2/H_3$ receptor classification system (Raible *et al.,* 1994). Histamine also activates human alveolar macrophages to release β-glucuronidase, and this effect is mediated by H_1 receptors (Cluzel *et al.,* 1990). Histamine stimulates suppressor T lymphocytes via H_2 receptors, and there is some evidence that this function may be depressed in atopic individuals (Beer *et al.,* 1982). IgE-mediated release of histamine from human basophils is inhibited by histamine itself acting via H_2 receptors, although it is possible that H_3 receptors are involved, because inhibition is seen with impromidine, which is now recognized to have H_3 receptor-blocking effects. Therefore, H_2 receptor antagonists may theoretically increase histamine release after allergen challenge, although H_2 receptors have not been demonstrated in mast cells of human lung. Furthermore, a decrease, rather than an increase, in responsiveness to inhaled allergen after chronic treatment with cimetidine has been reported (Bergstrand *et al.,* 1985).

H_3 agonists inhibit the release and synthesis of histamine in central neurons (Schultz *et al.,* 1991). It is possible that H_3 receptors may similarly inhibit the synthesis and release of histamine in lung mast cells. Allergen-induced bronchoconstriction in sensitized guinea pigs is enhanced by thioperamide but is unaffected by cimetidine, whereas it is almost completely abolished by mepyramine (Ichinose and Barnes, 1990b). Because thioperamide has no effect on histamine-induced bronchoconstriction, this strongly suggests that histamine released from pulmonary mast cells by allergen challenge normally inhibits further release via H_3 receptors on mast cells (autoinhibition). Histamine inhibits the release of tumor necrosis factor (TNF)-α from rodent mast cells, and this appears to be mediated by H_2 and H_3 receptors (Bissonnette, 1996). When these receptors are inhibited, this results in enhanced histamine release. Whether H_3 receptors are important in regulating the synthesis of histamine in these cells is not yet known, and it is also uncertain whether H_3 receptors are expressed in human mast cells.

4. Role in asthma.

a. RELEASE. Measurement of histamine in the circulation is complicated by the spontaneous release from basophils, and measurement of stable metabolites in the urine may not reflect release from mast cells in the airways. Several previous studies demonstrated elevations of plasma histamine concentrations in patients with asthma, at rest, after exercise, at night, and after allergen challenge, but these studies are difficult to interpret because of the likelihood of contamination from basophil release in the collected blood samples (Ind *et al.,* 1983). It is possible that basophils from patients with asthma may be more "leaky" and that this may contribute to the higher concentrations measured in asthmatic patients. Studies of histamine infusions in normal volunteers have demonstrated that doses of histamine that yield the plasma concentrations reported in patients with asthma have marked cardiovascular effects, indicating that the higher levels seen in the blood of asthmatic patients are likely to be generated in vitro during storage and preparation of the plasma samples. The histamine released from the airways may increase plasma concentrations, but this may be overwhelmed by the contribution from circulating basophils. Sampling closer to the site of histamine release may overcome these problems. Venous sampling in the arm shows an increase in plasma histamine concentrations after mast cell degranulation in the skin of the arm, induced by SP (Barnes *et al.,* 1986), but such sampling is not feasible in the airways. Measurement of histamine in bronchoalveolar lavage fluid is likely to provide a much more direct measurement of airway histamine release. There is evidence that histamine concentrations are elevated in bronchoalveolar lavage fluid of asthmatic patients,

both at rest and after allergen challenge (Liu *et al.,* 1991; Wenzel *et al.,* 1988). The source of histamine is presumed to be mucosal mast cells, and the contribution of infiltrating basophils is unclear.

b. EFFECTS OF INHIBITORS. Histamine mediates most of its effects on airway function via H_1 receptors, suggesting that H_1 antagonists may have therapeutic effects in airway disease. Nonsedating potent H_1 receptor antagonists, such as terfenadine, loratidine, and astemizole, may be given in large doses but, although these antihistamines have useful clinical effects in allergic rhinitis, they are far from effective for asthmatic patients, as demonstrated in a recent meta-analysis of clinical trials (Van Ganse *et al.,* 1997). The effects of antihistamines, even when taken in high doses, are small and clinically insignificant (Simmons and Simons, 1994). Terfenadine causes approximately 50% inhibition of the immediate response to allergen but has no effect on the late response. Antihistamines cause a small degree of bronchodilation in asthmatic patients, indicating a certain degree of histamine "tone," presumably resulting from the basal release of histamine from activated mast cells, as discussed above. Chronic administration of terfenadine has a small clinical effect among patients with mild allergic asthma (Taytard *et al.,* 1987) but is far less effective than other antiasthma therapies; therefore, these drugs cannot be recommended for the routine management of asthma. Some new antihistamines, such as cetirizine and azelastine, have been shown to have beneficial effects in asthma (Spector *et al.,* 1995; Busse *et al.,* 1996), but this may be unrelated to their H_1 antagonist effects (Walsh, 1994).

H_2 antagonists, such as cimetidine and ranitidine, may be contraindicated in asthma on theoretical grounds, if H_2 receptors are important in counteracting the bronchoconstricting effect of histamine. In clinical practice, however, there is no evidence that H_2 antagonists have any deleterious effect in asthma.

H_3 receptor agonists may have some theoretical benefit in asthma, because they may modulate cholinergic bronchoconstriction and inhibit neurogenic inflammation. Although (*R*)-α-methylhistamine relaxes rodent peripheral airways in vitro (Burgaud *et al.,* 1992), it has no effect, when given by inhalation, on airway caliber or metabisulfite-induced bronchoconstriction in asthmatic patients, indicating that a useful clinical effect is unlikely (O'Connor *et al.,* 1993).

c. CONCLUSIONS. Histamine is produced from mast cells in asthmatic airways and exerts many effects that are relevant to the pathophysiological mechanisms of asthma, including bronchoconstriction, plasma exudation, and mucus secretion. There is also evidence for an effect on the inflammatory process, particularly eosinophils. However, antihistamine H_1 antagonists have been disappointing in asthma therapy, and this presumably reflects the fact that all of the actions of histamine are mimicked by other mediators. New and more potent antihistamines appear to have greater beneficial effects in asthma, so that histamine may have a more important role than previously recognized.

B. Serotonin (5-Hydroxytryptamine)

Serotonin [5-hydroxytryptamine (5-HT)] causes bronchoconstriction in most animal species, but interest in this mediator is minimal because it is not a constrictor of human airways and its relevance in asthma seems doubtful (Barnes *et al.,* 1988).

1. Synthesis and metabolism. Serotonin is formed by decarboxylation of tryptophan (obtained in the diet) and is stored in secretory granules. Serotonin is present in mast cell granules from rodents but not humans. The major source of serotonin in humans is platelets, but serotonin is also found in neuroendocrine cells of the respiratory tract and has been localized to peripheral nerves.

2. Receptors. Multiple serotonin receptors have now been recognized, based on the development of selective antagonists and molecular cloning (Saxena, 1995). There are up to seven types of 5-HT receptors, each with several subtypes. Selective antagonists have now become available for clinical use, but few have been used in investigations of human airway cells or in the treatment of patients with asthma.

3. Effects on airways. Serotonin does not constrict human airway smooth muscle in vitro and may even have bronchodilating effects, although pulmonary vessels are constricted as expected (Raffestin *et al.,* 1985). In animals, serotonin increases acetylcholine release from airway nerves, and this has been demonstrated in human airways (Takahashi *et al.,* 1995). The receptor mediating this response appears to be a 5-HT_3 receptor (Takahashi *et al.,* 1995). In guinea pig airways, serotonin inhibits nonadrenergic noncholinergic (NANC), neurally induced constriction resulting from tachykinin release via a 5-HT_1-like receptor localized to sensory nerve endings (Ward *et al.,* 1994; Dupont *et al.,* 1996). In humans, infused serotonin has no effect on airway function but may have an inhibitory effect on cough reflexes, possibly mediated by receptors on airway sensory nerves (Stone *et al.,* 1993). Serotonin is a potent inducer of microvascular leakage in rodent airways, but it is not certain whether serotonin has this property in human airways. Serotonin has a blocking effect on sodium channels in human airway epithelial cells, but the receptor subtype involved has not been established (Graham *et al.,* 1992).

4. Role in asthma. Plasma serotonin levels are reported to be elevated in asthma and are significantly related to asthma severity (Lechin *et al.,* 1996). The source of serotonin is likely to be platelets, but the clinical relevance of this observation is unclear.

In animals, serotonin constricts airways via activation of 5-HT_2 receptors on airway smooth muscle cells. The 5-HT_2 receptor antagonist ketanserin has no effect on

airway function but exerts a small inhibitory effect on methacholine-induced bronchoconstriction in asthmatic patients (Cazzola *et al.,* 1990). Inhaled ketanserin has no effect on histamine-induced bronchoconstriction but exerts a small inhibitory effect on adenosine-induced bronchoconstriction, indicating a possible action on mast cells (Cazzola *et al.,* 1992).

C. Adenosine

1. Synthesis and metabolism. Adenosine is a purine nucleoside that is produced by dephosphorylation of 5′-AMP by the membrane-associated enzyme 5′-nucleotidase and is liberated intracellularly by cleavage of the high energy bonds of adenosine triphosphate, adenosine diphosphate, and cyclic 5′-AMP. However, during hypoxia or even excessive cell stimulation, when the utilization of energy and oxygen exceeds the supply, 5′-AMP is metabolized to adenosine (Mentzer *et al.,* 1975). This conversion is performed by extracellular 5′-nucleotidase. Adenosine release was originally demonstrated during myocardial hypoxia (Mentzer *et al.,* 1975), although there is now evidence that all cells are capable of producing adenosine in times of energy deficit. Adenosine can be released by lung tissue in times of hypoxia, such as after allergen-induced bronchoconstriction, when the circulating levels of adenosine have been shown to be 3 times the base-line concentrations (Mann *et al.,* 1986). Mast cells are a likely source of adenosine in this situation, because these cells have been shown to be capable of releasing adenosine in response to IgE cross-linking and other stimuli for mast cell activation (Marquardt *et al.,* 1986).

2. Receptors. Three distinct subtypes of receptor have been characterized to date, based on biochemical, functional, and more recent cloning studies (Linden *et al.,* 1991; Linden, 1994). These receptors include the A_1, A_{2a}, A_{2b}, and A_3 receptor subtypes. Interaction of adenosine with these receptors leads to either inhibition of adenylyl cyclase (A_1), stimulation of adenylyl cyclase (A_{2a} and A_{2b}) (Collis and Hourani, 1993), or activation of phospholipase C (A_3) (Ali *et al.,* 1990). The A_1 receptor is expressed in lung tissue (Ren and Stiles, 1994) and, in particular, A_1 receptors have been identified on human epithelial cells (McCoy *et al.,* 1995). The classification of adenosine receptors into A_{2a} and A_{2b} subtypes is based on distinct rank orders of potency of a range of agonists and antagonists and distinct nucleotide sequences of the two complementary deoxyribonucleic acids (cDNAs). A_{2a}, A_{2b}, and A_3 receptors are expressed in several tissues, including lungs, and in mast cells and fibroblasts (Linden *et al.,* 1993; Auchampach *et al.,* 1997; Ciruela *et al.,* 1997; Shryock and Belardinelli, 1997; Fredholm, 1997).

3. Effects on airways.

a. AIRWAY SMOOTH MUSCLE. Adenosine elicits little or no contraction of human bronchi from nonasthmatic subjects but potently constricts asthmatic airways in vitro (Björck *et al.,* 1992). This constriction is blocked by histamine and LT antagonists and is therefore likely to be attributable to the release of mediators from mast cells in asthmatic airways. It is likely that the bronchoconstricting effects of adenosine are indirect, resulting from the activation of mast cell degranulation, because adenosine causes histamine release from mast cells (Church *et al.,* 1986). Comparable results have been observed in vivo, where adenosine and AMP are able to elicit bronchoconstricting effects in atopic and asthmatic subjects but have no effect in normal subjects (Cushley *et al.,* 1983). Furthermore, dipyridamole (an inhibitor of adenosine uptake into tissues) enhances adenosine-induced bronchospasm in asthmatic subjects (Crimi *et al.,* 1988), an effect that can be inhibited by theophylline (a nonselective adenosine antagonist) (Cushley *et al.,* 1984). The receptor mediating the bronchoconstricting effect of adenosine in asthma is not yet known. In rabbits, the A_1 receptor is a likely candidate, because tracheal strips from rabbits immunized with house dust mites are more responsive to adenosine and the adenosine A_1-selective agonist cyclopentyladenosine than are tracheal strips isolated from naive animals (Ali *et al.,* 1994a). Furthermore, immunized animals are considerably more responsive to the bronchoconstricting effects of adenosine (Thorne and Broadley, 1994) and cyclopentyladenosine in vivo (Ali *et al.,* 1994b; el Hashim *et al.,* 1996). No bronchoconstricting effects of the A_3-selective agonist aminophenylethyladenosine have been found in rabbits (el Hashim *et al.,* 1996) or guinea pigs (Hannon *et al.,* 1995), although studies in rats have shown that aminophenylethyladenosine can elicit bronchoconstriction (Meade *et al.,* 1996). The histamine-releasing effect of adenosine may involve the A_{2b} receptor, because this effect is sensitive to enprofylline (an A_{2b} receptor antagonist) (Feoktistov and Biaggioni, 1995). Certainly, there is clinical evidence showing that elevated levels of histamine can be demonstrated in plasma after the inhalation of AMP by atopic subjects (Phillips *et al.,* 1990), and increased levels of histamine have been detected after the instillation of AMP directly into the airways (Polosa *et al.,* 1995). Furthermore, the H_1 receptor antagonist terfenadine has a protective effect against adenosine-induced bronchoconstriction in asthmatic subjects (Rafferty *et al.,* 1987).

b. VESSELS. Adenosine has been shown to have a wide range of effects in the cardiovascular system, which are well beyond the scope of this review (Olsson and Pearson, 1990). However, in the context of asthma, adenosine acting as a vasodilator can function synergistically with several inflammatory mediators, leading to increased vascular permeability. If adenosine release occurs in the vicinity of degranulating mast cells, such interactions may contribute to the edema that accompanies allergic responses in the airway.

c. NERVES. Another possible explanation for adenosine-induced bronchoconstriction is that it occurs sec-

ondarily to the activation of a neuronal reflex. Adenosine and related molecules have long been known to modulate synaptic transmission, although adenosine has been reported not to influence cholinergic responses in human trachea (Bai *et al.,* 1989) or contraction of guinea pig trachea induced by electrical field stimulation (Grundström *et al.,* 1981). Data obtained from in vivo experiments are inconclusive; some investigators failed to show any effect of the muscarinic receptor antagonist ipratropium bromide on the airway effects of inhaled adenosine (Mann *et al.,* 1985), whereas other groups observed a significant effect of atropine or ipratropium bromide on adenosine-induced bronchoconstriction (Crimi *et al.,* 1992). Furthermore, it has been suggested that AMP-induced effects in the airway may be secondary to the activation of sensory C-fibers (Polosa *et al.,* 1992b), a suggestion supported by clinical observations showing that the airway effects induced by inhaled adenosine or AMP can be inhibited by sodium cromoglycate and nedocromil sodium (drugs that can attenuate C-fiber function). The neutral endopeptidase (NEP) inhibitor phosphoramidon, which should enhance tachykinin-mediated effects, also has no effect on adenosine-induced bronchoconstriction responses (Polosa *et al.,* 1997b).

d. INFLAMMATORY CELLS. Adenosine is a potent mediator of mast cell degranulation, as described above, and therefore may contribute to the inflammatory changes observed in asthma. On the other hand, adenosine inhibits eosinophil degranulation (Yukawa *et al.,* 1989). A_3 receptors have been recently identified on human eosinophils (Walker *et al.,* 1997), and activation of these receptors by adenosine inhibits eosinophil migration (Knight *et al.,* 1997). Activation of A_3 receptors on eosinophils has also been shown to lead to an increase in $[Ca^{2+}]_i$ (Kohno *et al.,* 1996).

4. Role in asthma.

a. RELEASE. Increased levels of adenosine have been found in bronchoalveolar lavage fluid obtained from asthmatic subjects, compared with normal subjects (Driver *et al.,* 1993), and, as discussed above, adenosine concentrations in plasma are higher in allergic patients minutes after allergen provocation (Mann *et al.,* 1986). A_3 receptor expression is increased in asthmatic lungs, compared with lungs of normal subjects, although, because the A_3 receptor is expressed predominantly in eosinophils, this may be a reflection of eosinophilic infiltration (Walker *et al.,* 1997).

b. EFFECTS OF INHIBITORS. No specific receptor antagonists for adenosine have been evaluated against adenosine-induced bronchoconstriction in humans. Dipyridamole (an inhibitor of adenosine uptake) enhances adenosine-induced bronchospasm in asthmatic patients when administered intravenously or by inhalation (Crimi *et al.,* 1988), an effect that can be inhibited by theophylline (an adenosine receptor antagonist) (Cushley *et al.,* 1984). Adenosine-induced bronchospasm can also be inhibited by a variety of other drugs, including the H_1 antagonist terfenadine (Rafferty *et al.,* 1987), the cyclooxygenase (COX) inhibitor indomethacin (Crimi *et al.,* 1989), and sodium cromoglycate (Crimi *et al.,* 1988), although this does not provide direct evidence for the involvement of adenosine in asthma. Because theophylline has other actions (including nonselective phosphodiesterase inhibition) that may contribute to its anti-asthma effect, these findings cannot be taken as evidence for a role for adenosine, and studies with more selective adenosine antagonists are needed.

The role of endogenous adenosine in allergic responses has not been evaluated because of the lack of suitable drugs to test. However, the recent discovery that enprofylline is a selective A_{2b} receptor antagonist has provided a possible tool to evaluate the role of adenosine in allergic responses (Feoktistov and Biaggioni, 1995). This observation also raises the distinct possibility that some of the therapeutic activity of enprofylline and other xanthines, such as theophylline, may in part be related to inhibition of adenosine receptors (Pauwels and Joos, 1995). Furthermore, recent studies using an antisense oligonucleotide against the A_1 receptor showed that a reduction in A_1 receptors had a very significant effect on allergen-induced bronchospasm and bronchial hyperresponsiveness to inhaled histamine in an allergic rabbit model (Nyce and Metzger, 1997). Such results, if confirmed in human studies, would suggest that the A_1 receptor may play an important role in the pathogenesis of allergic airway disease.

c. CONCLUSIONS. Adenosine is likely to play some role in asthma, because it is produced as part of the stress response and this may be particularly important during exacerbations. Its effects in asthma are largely explained by an effect on sensitized mast cells, via A_{2b} receptors, and this appears to be specific for asthma. The mechanism by which A_{2b} receptors are expressed or activated in asthma is not yet known, but there is a strong indication that the development of a specific A_{2b} receptor antagonist may be useful in asthma

III. Lipid-Derived Mediators

A. Prostanoids

Prostanoids include PGs and thromboxane (Tx), which are generated from arachidonic acid, usually by the action of COX (PGH_2 synthase).

1. Synthesis and metabolism. Prostanoids are generated from arachidonic acid by two forms of COX (Mitchell *et al.,* 1995). COX-1 is constitutive and is responsible for basal release of prostanoids, whereas COX-2 is inducible by inflammatory stimuli, such as endotoxin and proinflammatory cytokines, and its induction is inhibited by glucocorticoids. Both COX-1 and COX-2 are expressed in human lung (Demoly *et al.,* 1997). Human airway epithelial cells basally express COX-1, whereas COX-2 is induced by IL-1β and TNF-α (Mitchell *et al.,*

1994; Newton *et al.,* 1997b; Asano *et al.,* 1997) and is enhanced by NO (Watkins *et al.,* 1997). COX-2 is also induced in cultured human airway smooth muscle cells by proinflammatory cytokines and bradykinin (Belvisi *et al.,* 1997; Pang and Knox, 1997a,b), and the formation of prostanoids is blocked by the selective COX-2 inhibitor L745,337 (Saunders *et al.,* 1998). COX-2 expression is inhibited by dexamethasone in both epithelial cells and smooth muscle cells. The induction of COX-2 is regulated in part by NF-κB, and this may also account for the inhibitory action of glucocorticoids (Newton *et al.,* 1997a). There is no difference in the profiles of prostanoids formed by COX-1 and COX-2. In epithelial cells and airway smooth muscle cells, the predominant prostanoids are PGE_2 and 6-keto-$PGF_{1\alpha}$ (metabolite of PGI_2), whereas there is relatively little formation of Tx (Mitchell *et al.,* 1994; Belvisi *et al.,* 1997). Tx is formed from the intermediate PGH_2 by a distinct enzyme, Tx synthase, which has been cloned (Ohashi *et al.,* 1992).

Recently, a novel nonenzymatic pathway for prostanoid formation was described. Isoprostanes are generated by lipid peroxidation of arachidonic acid by oxidative stress (Morrow and Roberts, 1996). The most prevalent isoprostane in humans is 8-epi-$PGF_{2\alpha}$, which is a potent constrictor of human airways in vitro (Kawikova *et al.,* 1996). All cells in the airway have the capacity to release prostanoids, but the profile of prostanoids released depends on the cell type and on the form of cell stimulation, as discussed below.

2. Receptors. Several prostanoid receptors have now been cloned (Ushikubi *et al.,* 1995; Pierce *et al.,* 1995). Pharmacologically, prostanoid receptors are classified according to the prostanoid that causes selective activation; PGE_2 preferentially activates EP receptors, PGI_2 (prostacyclin) activates IP receptors, $PGF_{2\alpha}$ activates FP receptors, PGD_2 activates DP receptors, and Tx activates TP receptors (Coleman *et al.,* 1994). Within each receptor type there may be distinct subtypes, many of which have been identified using selective ligands and cloning; the EP receptor has at least four subtypes, which are differentially expressed in different cell types. EP_1 receptors mediate activation responses and are involved in hyperalgesic responses, whereas EP_2 and EP_4 receptors mediate smooth muscle relaxation responses and EP_3 receptors modulate neurotransmitter release. In airway smooth muscle, several constrictor PGs (PGD_2, $PGF_{2\alpha}$, and 8-epi-$PGF_{2\alpha}$) appear to work through activation of TP receptors (Coleman and Sheldrick, 1989; Kawikova *et al.,* 1996).

3. Effects on airways.

a. AIRWAY SMOOTH MUSCLE. PGE_2 relaxes human airway smooth muscle in vitro via EP receptors (Knight *et al.,* 1995). The relaxation response to PGE_2 in human airways is mediated by EP_2 receptors (McKenniff *et al.,* 1988), but in animal airways an EP_1 receptor subtype is also involved (Ndukwu *et al.,* 1997). Inhaled PGE_2 causes bronchodilation in normal subjects (Walters and Davies, 1982) but may cause constriction in patients with asthma because of activation of reflex cholinergic bronchoconstriction. Inhaled PGE_2 protects against exercise-, metabisulfite-, and allergen-induced bronchoconstriction in asthmatic patients, however (Melillo *et al.,* 1994; Pavord *et al.,* 1992, 1993). PGI_2 is less potent than PGE_2 in relaxing human airways in vitro (Tamaoki *et al.,* 1993) and, in contrast to PGE_2, does not protect against histamine-induced contraction (Knight *et al.,* 1995). Inhaled PGI_2 has little effect on airway function (Hardy *et al.,* 1985).

In contrast, $PGF_{2\alpha}$, PGD_2, 8-epi-$PGF_{2\alpha}$, and Tx cause bronchoconstriction of human airways in vitro, and all are antagonized by TP receptor antagonists (Coleman and Sheldrick, 1989; Kawikova *et al.,* 1996). Both $PGF_{2\alpha}$ and PGD_2, when inhaled, cause bronchoconstriction in asthmatic patients (Hardy *et al.,* 1984; Fish *et al.,* 1984). The stable Tx analogue U46619 is a potent constrictor in asthmatic patients, and this effect is mediated in part via acetylcholine release (Jones *et al.,* 1992; Saroea *et al.,* 1995). There is considerable evidence obtained with animals to suggest that TxA_2 is involved in airway hyperresponsiveness, but this is not supported by studies in asthmatic patients (O'Byrne and Fuller, 1989).

Prostanoids also have effects on airway smooth muscle proliferation. PGE_2 inhibits proliferation of human airway smooth muscle in vitro after stimulation with fetal calf serum or growth factors (Johnson *et al.,* 1995; Panettieri *et al.,* 1995); because PGE_2 is the major product of COX-2 induced by inflammatory stimuli in human airway smooth muscle, this provides an inhibitory feedback mechanism (Saunders *et al.,* 1998). Tx increases proliferation of rabbit airway smooth muscle (Noveral and Grunstein, 1992).

b. VESSELS. PGE_2 and PGI_2 are vasodilators and therefore should theoretically increase leakage in asthmatic airways. Tx is a potent vasoconstrictor, but it potently increases plasma exudation in guinea pig airways (Lötvall *et al.,* 1992; Tokuyama *et al.,* 1992). The isoprostane 8-epi-$PGF_{2\alpha}$, like Tx, increases plasma exudation in rodent airways (Okazawa *et al.,* 1997).

c. SECRETIONS. Prostanoids stimulate airway mucus secretion in various animal species, but few studies have been conducted in human airways.

d. NERVES. PGE_2 inhibits cholinergic nerve constriction of human airways in vitro at concentrations lower than those that cause bronchoconstriction, suggesting that there is an inhibitory effect on acetylcholine release, presumably mediated by an EP_3 receptor (Ellis and Conanan, 1996). In animals, this has been confirmed by measurements of acetylcholine after neural stimulation (Barnes, 1992a). In rat airways, PGE_2 also inhibits neurogenic inflammation, suggesting an inhibitory action on tachykinin release from sensory nerves (Morikawa *et al.,* 1992). Inhaled PGE_2 causes coughing in normal and asthmatic subjects and increases the sensitivity of the cough reflex (Chaudry *et al.,* 1989; Stone *et*

al., 1992). This may be mediated by EP_1 receptors. In addition, PGE_2 inhalation increases the sensation of dyspnea (Taguchi *et al.,* 1992). $PGF_{2\alpha}$ also induces coughing but does not appear to sensitize the cough reflex (Stone *et al.,* 1992). Tx increases the release of acetylcholine from cholinergic nerves in animals in vitro (Chung *et al.,* 1985), and the bronchoconstriction response to inhaled U46619 is attenuated by prior treatment with a cholinergic antagonist (Saroea *et al.,* 1995).

e. INFLAMMATORY CELLS. Prostanoids have effects on the release of inflammatory mediators from inflammatory cells. This has been most carefully studied with PGE_2, which inhibits the release of mediators from mast cells, monocytes, neutrophils, and eosinophils (Giembycz *et al.,* 1990; Peters *et al.,* 1982; Talpain *et al.,* 1995; Meja *et al.,* 1997). The EP receptors involved are probably EP_2 receptors. The effect of PGE_2 on T lymphocytes is less clearly delineated; PGE_2 favors the development of helper T (Th)2 cells by inhibiting IL-2 and interferon (IFN)-γ production in human $CD4^+$ cells (Hilkens *et al.,* 1995) and inhibiting the secretion of IL-12 from macrophages (Van der Pouw Kraan *et al.,* 1995). Furthermore, culture of dendritic cells in the presence of PGE_2 results in Th2 cell differentiation and increased synthesis of IL-5 (Kalinski *et al.,* 1997). However, with an allergen challenge, inhaled PGE_2 protects against the late response as well as the early response, suggesting that its anti-inflammatory action against eosinophils may predominate over its T cell action (Pavord *et al.,* 1993). The effects of other prostanoids on inflammatory cells are less clear. Tx causes airway hyperresponsiveness in animal models, but this has not been seen in human studies with inhaled U46619 (Jones *et al.,* 1992).

4. Role in asthma.

a. RELEASE. Bronchoalveolar lavage studies have demonstrated increased concentrations of $PGF_{2\alpha}$, PGD_2, and TxB_2 in patients with asthma (Liu *et al.,* 1990; Oosterhoff *et al.,* 1995; Dworski *et al.,* 1994; Smith *et al.,* 1992). PGD_2 is the prostanoid present in highest concentration, and this is correlated with an increase in mast cell tryptase, indicating the likely mast cell origin of the mediator. After allergen challenge, there is an increase in PGD_2 and TxB_2 levels (Dworski *et al.,* 1994). A urinary metabolite of Tx (11-dehydro-TxB_2) is increased in asthmatic subjects after challenge with allergen (Kumlin *et al.,* 1992). COX-2 shows increased expression in the airways of asthmatic patients and is presumably induced by proinflammatory cytokines (Demoly *et al.,* 1997). In peripheral leukocytes of asthmatic patients, there is increased expression of COX-1 and COX-2 mRNA (Kuitert *et al.,* 1996).

b. EFFECTS OF INHIBITORS. Nonselective COX inhibitors, including aspirin and flurbiprofen, have little or no beneficial effect in challenge studies or in the treatment of clinical asthma, but this may be because they block production of both bronchoconstricting (PGD_2, $PGF_{2\alpha}$, and TxA_2) and bronchodilating (PGE_2 and PGI_2) mediators. Specific Tx synthase inhibitors have been developed for use in asthma. Ozagrel (ONO-046), a moderately potent orally active Tx synthase inhibitor, reduces airway hyperresponsiveness to cholinergic agonists when given orally or by aerosol, but the effect is very small and unlikely to be of clinical significance (Fujimura *et al.,* 1990a,b). Another, more potent, Tx synthase inhibitor, pirmagrel (CGS13080), completely prevents the increase in serum TxB_2 levels after allergen challenge in asthmatic patients. Although it causes a very small reduction in the early response to allergen, there is no effect on the late response or on airway hyperresponsiveness (Manning *et al.,* 1991). Several TP receptor antagonists have also been studied in asthma and have the advantage over Tx synthase inhibitors that they inhibit the bronchoconstricting effects of $PGF_{2\alpha}$, PGD_2, and 8-epi-$PGF_{2\alpha}$, in addition to TxA_2. Vapiprost (GR32191) has no effect on airway hyperresponsiveness in asthmatic patients after 3 weeks of administration (Stenton *et al.,* 1992) and no effect in exercise-induced asthma (Finnerty *et al.,* 1991), whereas another TP receptor antagonist, ramatroban (Bay u3405), has a small effect on methacholine responsiveness (Aizawa *et al.,* 1996). However, ramatroban is ineffective against exercise-induced asthma, at a dose that blocks PGD_2-induced bronchoconstriction, and is ineffective against histamine and bradykinin challenge (Magnussen *et al.,* 1992; Johnston *et al.,* 1992; Rajakulasingam *et al.,* 1996). The potent TP receptor antagonist seratrodast has a small bronchodilating effect after prolonged administration (Samara *et al.,* 1997). Overall, neither Tx synthase inhibitors nor receptor antagonists have useful clinical effects in asthma, suggesting that bronchoconstrictor prostanoids do not play a major role in the pathophysiological mechanisms of asthma.

PGE_2, in contrast, may be important in protecting against bronchoconstriction and controlling the inflammatory response (Pavord and Tattersfield, 1995). Inhibition of PGE_2 formation by COX inhibitors may therefore be potentially detrimental. Indeed, in a small proportion of asthmatic patients, aspirin and other nonselective COX inhibitors induce asthma (Szczeklik, 1997). Aspirin challenge in aspirin-sensitive patients inhibits the formation of PGE_2 and increases LT formation but, surprisingly, also increases concentrations of PGD_2 and $PGF_{2\alpha}$ (Szczeklik *et al.,* 1996b). PGE_2 inhalation protects against asthma induced by inhaled lysine-aspirin in aspirin-sensitive asthmatic patients (Szczeklik *et al.,* 1996a). Selective COX-2 inhibitors, such as L745,337 and A398, may also prove to be safe in patients with aspirin-sensitive asthma, because it is possible that bronchoconstriction in these patients may be the result of inhibition of PGE_2 synthesis by COX-1. Nimesulide, a COX-2 selective blocker, is reported to be well tolerated in aspirin-sensitive asthmatics (Senna *et al.,* 1996). PGE_2 may have additional therapeutic potential in asthma, but its tendency to induce coughing is a

serious limitation. Because the receptors on sensory nerves (probably EP_1 receptors) differ from those that mediate bronchodilation and inhibition of anti-inflammatory effects (mainly EP_2 receptors), selective EP agonists (such as butaprost) may be more useful.

c. CONCLUSIONS. Prostanoids are produced in asthmatic airways and appear to have several effects on the airways, including bronchoconstriction, plasma exudation, sensitization of nerve endings, and effects on inflammatory cells, which are mediated by prostanoid receptors. However, inhibition of their formation with COX or Tx synthase inhibitors or inhibition of TP receptors does not appear to benefit asthmatic patients. One possibility is that COX inhibitors, while blocking the formation of bronchoconstricting prostanoids (PGD_2, $PGF_{2\alpha}$, and TxA_2), also inhibit the formation of the bronchodilating PGs (PGE_2 and PGI_2), which may counteract these effects. Furthermore, isoprostanes may be formed in response to oxidative stress in asthma, and their formation occurs independently of COX function.

B. Leukotrienes

There is increasing evidence that LTs play an important role in the pathophysiological changes of asthma. This has mainly been provided by studies with potent inhibitors of LT receptors, which are now in clinical use for asthma therapy.

1. Synthesis and metabolism. LTs are potent lipid mediators produced by arachidonic acid metabolism in cell or nuclear membranes. They are derived from arachidonic acid, which is released from membrane phospholipids via the activation of phospholipase A_2. Arachidonic acid is subsequently metabolized by the enzyme 5-LO, to produce LTs. The free 5-LO enzyme is found in the cytoplasm and cannot metabolize arachidonic acid. However, after the free 5-LO has been activated, it is translocated to the nuclear membrane, where a membrane-bound protein termed 5-LO-activating protein stabilizes the translocated 5-LO, thus allowing the transformation of arachidonic acid into LTA_4 (Evans *et al.,* 1991). Recently, a family of mutations of 5-LO genes have been reported in asthmatics. These are characterized by a variable number of tandem repeat segments in the promoter region, and they modify reporter gene transcription. This may account for differences in the susceptibility of patients to drugs modifying 5-LO activity (In *et al.,* 1997). LTA_4 is further metabolized to LTC_4 (via the activation of LTC_4 synthase) or to LTB_4 (by LTA_4 hydrolase). After release into the extracellular environment, LTC_4 can be further metabolized to LTD_4 and LTE_4 by cleavage of the peptide side chain of LTC_4. Several types of airway cells, including mast cells, eosinophils, macrophages, neutrophils, and epithelial cells, can synthesize LTs in response to a variety of stimuli. LTB_4, synthesized predominantly by LTA_4 hydrolase in neutrophils, is an extremely potent activator of neutrophils, causing aggregation, chemotaxis, and degranulation (Ford-Hutchinson, 1991; Brain and Williams, 1990). LTC_4, LTD_4, and LTE_4 are the active constituents of what was once termed "slow reacting substance of anaphylaxis."

2. Receptors. The biological effects of LTs occur through their ability to stimulate specific receptors, which have been identified on several cell types. There are probably multiple receptors, although two major classes have been well characterized. The BLT receptors are activated by LTB_4 and to a lesser extent by 20-OH-LTB_4 and 12-(*R*)-hydroxyeicosatetraenoic acid (HETE). The BLT receptor is a 60-kDa plasma membrane protein (Miki *et al.,* 1990) and has recently been cloned (Yokomizo *et al.,* 1997). Cys-LTs act via cys-LT receptors, of which two types have been pharmacologically characterized. Cys-LT_1 receptors mediate all of the known airway effects of cys-LTs in human cells (Coleman *et al.,* 1995). A second receptor type, the cys-LT_2 receptor, has been described on pulmonary veins, on the basis of responses to certain LT antagonists (Metters, 1995; Gorenne *et al.,* 1996). To date, none of these LT receptors has been cloned.

3. Effects on airways.

a. AIRWAY SMOOTH MUSCLE. Cys-LTs are very potent contractile agents for human bronchi in vitro, being approximately 1000 times more potent than histamine, and they elicit this effect via activation of cys-LT_1 receptors (Krell *et al.,* 1990). There is a certain degree of tone in human airways in vitro, and this is partly mediated by cys-LTs, because it can be reduced by 5-LO inhibitors and by cys-LT_1 receptor antagonists (Ellis and Undem, 1994). The ability of cys-LTs to act as potent bronchoconstricting agents has also been demonstrated in vivo, both in normal subjects and in patients with asthma (Drazen, 1988). Inhaled LTD_4 also increases the maximal airway narrowing induced by inhaled methacholine (Bel *et al.,* 1987), and LTE_4 induces airway hyperresponsiveness to inhaled histamine, an effect that may persist for several days (Arm *et al.,* 1988; O'Hickey *et al.,* 1991). LTB_4 has no direct effect on human airway smooth muscle and does not cause bronchodilation after inhalation in asthmatic patients, even when combined with PGD_2 (Black *et al.,* 1989a). Cys-LTs may also stimulate airway smooth muscle proliferation (Cohen *et al.,* 1995), although this has not yet been shown for human airway smooth muscle and may be secondary to release of Tx.

b. VESSELS. Cys-LTs potently elicit increased vascular permeability in airways, leading to airway edema (Arakawa *et al.,* 1993; Henderson, 1994). The potential importance of allergen-induced edema in the airways has been demonstrated with the use of 5-LO inhibitors in experimental animals (Hui *et al.,* 1991), although such studies have yet to be performed with asthmatic patients.

c. SECRETION. Cys-LTs increase mucus secretion, both directly via effects on goblet cells and submucosal gland cells (Hoffstein *et al.,* 1990; Goswami *et al.,* 1989) and

indirectly via the activation of airway nerves, leading to reflex secretion from submucosal glands (Marom *et al.,* 1982).

d. NERVES. In guinea pigs, LTD_4-induced bronchoconstriction and plasma exudation are partly mediated by tachykinin release, suggesting that LTD_4 releases neuropeptides from sensory nerves (Ishikawa *et al.,* 1996). This is unlikely to be relevant in vivo in humans, because inhaled LTD_4 does not cause coughing and there is no effect of an anticholinergic drug on the bronchoconstriction response (Ayala *et al.,* 1988).

e. INFLAMMATORY CELLS. LTB_4 and 5-HETE are potent stimuli for leukocyte function, including chemotaxis and aggregation of polymorphonuclear leukocytes (Ford Hutchinson, 1990), effects that are mediated by activation of BLT receptors (Rola Pleszczynski and Stankova, 1992). Furthermore, LTB_4 elicits eosinophilic infiltration into guinea pig skin (Faccioli *et al.,* 1991) and airways (Silbaugh *et al.,* 1987) and is a potent activator of the oxidative burst in eosinophils (Perkins *et al.,* 1995). Specific inhibitors of 5-LO inhibit allergen-induced eosinophilic infiltration in guinea pig skin (Teixeira *et al.,* 1994) and airways (Tohda *et al.,* 1997) and in mouse airways, where they also block mucus secretion (Henderson *et al.,* 1996). Furthermore, LTB_4 antagonists block allergen-induced eosinophilic infiltration into guinea pig lungs (Richards *et al.,* 1989, 1991), although this finding has not been confirmed in other studies (Seeds *et al.,* 1995). In contrast to the potent effects of LTB_4 in guinea pig eosinophils, this mediator has little effect on human eosinophils.

Inhaled cys-LTs induce an eosinophil-rich infiltrate into the airways in experimental animals (Foster and Chan, 1991; Wegner *et al.,* 1993; Underwood *et al.,* 1996). This unexpected effect of cys-LTs appears to be the result of release of IL-5 (Underwood *et al.,* 1996). An eosinophil response to cys-LTs has also been observed in the lungs of a small group of asthmatic patients, both in airway biopsies (Laitinen *et al.,* 1993) and in induced sputum (Diamant *et al.,* 1997). This is consistent with reports that cys-LT antagonists reduce allergen-induced eosinophilic infiltration into the airways of experimental animals (Chan *et al.,* 1990; Nakagawa *et al.,* 1993), which suggests a potential anti-inflammatory effect of anti-LTs. This suggestion is supported by the observations that various 5-LO inhibitors can also inhibit allergen-induced eosinophilic infiltration into the airways of experiment animals (Gulbenkian *et al.,* 1990; Yeadon *et al.,* 1993; Richards *et al.,* 1989). Such observations have yet to be convincingly confirmed in asthma, although several preliminary studies have suggested that anti-LTs reduce the number of inflammatory cells in bronchoalveolar lavage fluid from allergic subjects undergoing segmental allergen challenge (Calhoun *et al.,* 1997) and reduce circulating blood eosinophil numbers (Reiss *et al.,* 1996). The 5-LO inhibitor zileuton has also been reported to reduce the number of eosinophils in circulating blood of patients with nocturnal asthma, with clinical improvement (Wenzel *et al.,* 1995), although a trial of the specific LTB_4 antagonist LY293111 indicated no clinical benefit in allergen-induced early or late responses (Evans *et al.,* 1996a), despite a reduction in neutrophil numbers.

4. Role in asthma.

a. RELEASE. In humans, elevated levels of cys-LTs have been detected in plasma, bronchoalveolar lavage fluid, and sputum samples obtained from asthmatics during spontaneous exacerbations of their asthma or after allergen exposure (Taylor *et al.,* 1989; Wenzel *et al.,* 1995). Furthermore, several groups have shown elevated levels of LTE_4 in the urine of allergic patients undergoing allergen exposure (Taylor *et al.,* 1989; Drazen *et al.,* 1992) and exhibiting nocturnal asthma (Bellia *et al.,* 1996). In another study, the increase in urinary LTE_4 levels in allergic asthmatics parallels the bronchoconstriction and subsides with resolution of the airway response (Kumlin *et al.,* 1992). Urinary LTE_4 levels are increased in aspirin-sensitive asthmatic patients (Kumlin *et al.,* 1992), supporting the view that in these patients aspirin produces its effect by increasing cys-LT production. This is consistent with the recent demonstration of increased LTC_4 synthase expression in bronchial biopsies of aspirin-sensitive asthmatics (Sampson *et al.,* 1997), and this may be linked to a polymorphism of the LTC_4 synthase gene (Sanak *et al.,* 1997).

b. EFFECTS OF INHIBITORS. Numerous clinical studies have been performed with cys-LT_1 receptor antagonists and 5-LO inhibitors (collectively termed anti-LTs) and support a role for cys-LTs in asthma (Chung, 1995; O'Byrne *et al.,* 1997; Smith, 1996). There are no clear differences between 5-LO inhibitors and cys-LT_1 receptor antagonists, suggesting that LTB_4 does not play a role in asthma. This is supported by the lack of effect of an LTB_4 antagonist in asthmatic patients, at least during allergen challenge (Evans *et al.,* 1996a). Several anti-LTs have been shown to improve base-line lung function in asthmatic patients (Hui *et al.,* 1991; Joos *et al.,* 1991; Kips *et al.,* 1991; Gaddy *et al.,* 1992; Israel *et al.,* 1993b; Reiss *et al.,* 1997) but not in nonasthmatic subjects (Smith *et al.,* 1990; Spencer *et al.,* 1991). This suggests that there is a certain degree of LT tone in asthmatic airways. The bronchodilating effect of anti-LTs, although modest, is additive with that of β_2-agonists (Hui *et al.,* 1991; Gaddy *et al.,* 1992), indicating that anti-LTs may inhibit some component of airway narrowing other than smooth muscle contraction (such as edema).

Several studies have shown the efficacy of anti-LTs during various provocation challenges. Anti-LTs protect against the early response to allergen in allergic asthmatics (Fuller *et al.,* 1989; Taylor *et al.,* 1991) and shift the allergen dose-response curve to the right approximately six-fold (Dahlen *et al.,* 1991), supporting a role for mast cell-derived LTs in allergen-induced broncho-

constriction (Holgate, 1996). The ability of anti-LTs to inhibit allergen-induced late responses is less certain, because of the change in base-line lung function. In a preliminary study with LY171883, no significant effect on the late response was observed (Fuller *et al.,* 1989), a finding confirmed by studies evaluating inhaled L-648,051 (Bel *et al.,* 1990). In contrast, the more potent antagonist zafirlukast and the 5-LO-activating protein inhibitor Bay x1005 appear to have some effect on the late response (Taylor *et al.,* 1991; Dahlen *et al.,* 1997). Anti-LTs also protect against cold air- and exercise-induced bronchoconstriction in asthmatic subjects (Israel *et al.,* 1990; Manning *et al.,* 1990; Robuschi *et al.,* 1992; Finnerty *et al.,* 1992; Makker *et al.,* 1993). Anti-LTs are particularly effective in blocking aspirin-induced asthma in aspirin-sensitive asthmatics, giving almost complete protection (Christie *et al.,* 1991; Yamamoto *et al.,* 1994; Israel *et al.,* 1993a; Dahlen *et al.,* 1993; Nasser *et al.,* 1994), and they also cause bronchodilation (Dahlen *et al.,* 1993).

There are now several well controlled studies with anti-LTs demonstrating clinical efficacy in patients with asthma. For example, zafirlukast reduces symptoms and improves lung function, in addition to reducing exacerbations (Barnes *et al.,* 1997; Spector *et al.,* 1994; Suissa *et al.,* 1997). Similar effects have been seen after regular treatment with montelukast (administered once-daily) and pranlukast (administered twice-daily) (Reiss *et al.,* 1998; Barnes *et al.,* 1997). The effects of LT antagonists are supported by similar effects of the 5-LO inhibitor zileuton (Israel *et al.,* 1993b, 1996; Fischer *et al.,* 1995; Dekhuijzen *et al.,* 1997). Furthermore, the addition of zileuton to therapy with low doses of inhaled corticosteroid resulted in greater control of asthma, compared with that achieved by increasing the dose of the inhaled steroid, suggesting that drugs affecting the synthesis or action of LTs may have biological activities complementary to those of the inhaled corticosteroids (O'Connor *et al.,* 1996). It is of interest that even high doses of inhaled or orally administered steroids do not reduce LT production in asthma, as measured by urinary LTE_4 excretion (Dworski *et al.,* 1994; O'Shaughnessy *et al.,* 1993); therefore, anti-LTs may be usefully added to inhaled corticosteroids for patients not achieving control with low doses.

One of the features of early studies of anti-LTs in asthma was the heterogeneity of responses, with some patients (approximately one-third) showing a very good response and others being apparently unresponsive. This presumably reflects the varying contributions of LTs in different patients and might be a reflection of polymorphism of the 5-LO gene (In *et al.,* 1997).

c. CONCLUSIONS. There is now substantial evidence that cys-LTs play an important role in asthma. Cys-LT production is increased in asthma in response to various challenges that worsen asthma. Cys-LTs are potent mediators of bronchoconstriction, plasma exudation, and mucus secretion, and there is now a growing body of evidence that they may also increase eosinophilic inflammation. The importance of cys-LTs in asthma has been highlighted by the clinical usefulness of LT receptor antagonists, which are now in routine use in several countries. This has been supported by similar clinical benefits of 5-LO inhibitors. Some patients, particularly those with aspirin-sensitive asthma, respond very well to anti-LTs, whereas others show little benefit, indicating that LTs play a variable role. Anti-LTs are less effective than corticosteroids in asthma treatment, suggesting that other inflammatory mediators play important roles in most patients. LTB_4 does not appear to play an important role in asthma, which is not surprising, because neutrophilic infiltration is not a feature of asthma in most patients.

C. Platelet-Activating Factor

PAF has long been implicated in the pathophysiological mechanisms of asthma, because exogenous PAF closely mimics many of the clinical features of asthma, including airway hyperresponsiveness.

1. Synthesis and metabolism. PAF is an ether-linked phospholipid (1-O-alkyl-sn-glycero-3-phosphocholine) that was first described as a substance released from IgE-stimulated basophils. The synthesis of PAF occurs in a wide variety of inflammatory cells, including platelets, neutrophils, basophils, macrophages, and eosinophils (Barnes *et al.,* 1989; Chung, 1992). The synthesis of PAF in inflammatory cells is generally via a two-step enzymatic pathway involving first the activation of phospholipase A_2, which cleaves a free fatty acid from ether-linked phospholipids (called plasmalogens) to yield lyso-PAF; under appropriate conditions, lyso-PAF can be acetylated, to form the biologically active PAF, by a rate-limiting enzyme that is termed acetyl transferase and is found in the cytoplasm of inflammatory cells (Barnes *et al.,* 1989). Large amounts of PAF can be synthesized by several inflammatory cell types in the lung, including resident cells such as mast cells (Triggiani *et al.,* 1991) and alveolar macrophages (Bratton *et al.,* 1994).

PAF is not a single, biologically active molecule; rather, several molecular species of PAF with significant biological activity are now known to exist (McManus *et al.,* 1993). For example, the ester-linked, 1-acyl species 1-palmitoyl-2-acetoyl-sn-glyceryl-3-phosphocholine (PAGPC) is synthesized by a wide variety of cells, including endothelial cells, basophils, mast cells, and lymphocytes (Columbo *et al.,* 1993; Triggiani *et al.,* 1991). PAGPC and related members of this family of lipids can interact with a G protein-linked receptor, with the acyl-PAFs being approximately 300 to 1000 times less potent than PAF (Columbo *et al.,* 1993; Tordai *et al.,* 1994). However, PAGPC can also act as a natural PAF receptor antagonist (Columbo *et al.,* 1993; Tordai *et al.,* 1994; Mazer *et al.,* 1998), raising the possibility that these

other forms of PAF may be involved as autoregulatory molecules for PAF.

The major enzyme responsible for the catabolism of PAF is PAF acetylhydrolase, a PAF-specific esterase that cleaves the acetyl group at the sn-2-position, producing lyso-PAF. PAF acetylhydrolase was initially described as being abundant in human plasma and was later shown to be associated with low density lipoproteins (Stafforini *et al.,* 1987). Since these early observations, acetylhydrolase has been described in various organs, including lung, kidney, brain, and liver (Venable *et al.,* 1993). There is now known to be an intracellular acetylhydrolase enzyme present in the cytoplasm of several inflammatory cell types, including mast cells, macrophages, and platelets. These cells can release acetylhydrolase and probably contribute to the extracellular acetylhydrolase content that has been identified in several biological fluids, such as skin (Teaford *et al.,* 1992) and nasal lavage fluid (Shin *et al.,* 1994; Touqui *et al.,* 1994), after allergen challenge. Furthermore, recent studies have identified an acetylhydrolase in bronchoalveolar lavage fluid that is distinct from either plasma acetylhydrolase or erythrocyte-derived acetylhydrolase (Triggiani *et al.,* 1997). This novel enzyme is calcium independent and has other characteristics that differentiate it from other forms of acetylhydrolase that have been identified (Triggiani *et al.,* 1997). This enzyme was present in smaller amounts in bronchoalveolar lavage fluid obtained from patients with mild asthma (Triggiani *et al.,* 1997), supporting previous studies showing reduced activity of plasma acetylhydrolase in young patients with moderate to severe asthma (Miwa *et al.,* 1988; Tsukioka *et al.,* 1996). It has been proposed that asthmatic patients have a genetic defect in plasma acetylhydrolase (Miwa *et al.,* 1988), although it is not yet clear what causes the reduced acetylhydrolase activity in bronchoalveolar lavage fluid. It is certainly not the presence of an inflammatory condition in the airway, because patients with fibrosis actually exhibited increased levels of acetylhydrolase in bronchoalveolar lavage fluid (Triggiani *et al.,* 1997). The deficiency of PAF acetylhydrolase in Japanese children is an autosomal recessive syndrome resulting from a missense mutation that abolishes enzymatic activity, but it is not clear whether this is associated with severe asthma (Stafforini *et al.,* 1996). A recombinant human PAF acetylhydrolase has been produced and has been shown to reduce PAF-induced inflammatory responses in the airways (Tjoelker *et al.,* 1995). Such observations suggest that local inactivation of PAF at local sites of inflammation might be a practical therapeutic approach.

2. Receptors. A PAF receptor has been cloned from human platelets and leukocytes and shown to be a typical G protein-linked receptor with seven transmembrane domains (Nakamura *et al.,* 1993; Shimizu and Izumi, 1995). PAF receptors are expressed in animal and human lung (Shirasaki *et al.,* 1994b). Recent evidence has shown that substitution of the Cys90, Cys95, or Cys173 residues in the PAF receptor with alanine or serine yields mutant receptors that do not bind PAF and are not expressed on the surface of cells but are found intracellularly (Le Gouill *et al.,* 1997). The cell signaling pathways initiated by PAF interactions with its receptor are well characterized and include increases in $[Ca^{2+}]_i$ (Mazer *et al.,* 1991), increases in IP_3 and diacylglycerol levels, and induction of cell cycle-active genes, such as *fos*, *jun*, and *egr*-1 (Mazer *et al.,* 1991; Schulam *et al.,* 1991). PAF also activates the transcription factor AP-1 in bronchial epithelial cells (Le Van *et al.,* 1998). The PAF receptor undergoes homologous desensitization by phosphorylation of cytoplasmic tail sites in the receptor molecule (Takano *et al.,* 1994), and related lipids such as PAGPC can also desensitize the classical PAF receptor (Mazer *et al.,* 1998). PAF exposure, however, leads to an increase in PAF receptor mRNA levels, suggesting increased turnover of the receptor (Shirasaki *et al.,* 1994a). Overexpression of the PAF receptor in transgenic mice results in airway hyperresponsiveness, which is attenuated by Tx, LT, and muscarinic antagonists (Nagase *et al.,* 1997).

Many PAF receptor antagonists have been identified and have facilitated the characterization of PAF receptors on a wide variety of inflammatory cells. However, there have been findings with certain PAF receptor antagonists that suggest that PAF may act via more than one receptor. Evidence from both human and animal studies suggests that there may be heterogeneity of PAF receptors (Hwang, 1990; Lambrecht and Parnham, 1986; Kroegel *et al.,* 1989). For example, PF10040 can antagonize PAF-induced edema formation (Rossi *et al.,* 1992) and PAF-induced bronchial hyperresponsiveness (Herd *et al.,* 1994) but has no effect on PAF-induced bronchoconstriction (Herd *et al.,* 1994). Furthermore, it has been demonstrated that only a small part of the total amount of PAF generated by cells is actually released, with intracellular PAF having been proposed to be a signaling molecule itself (Stewart and Harris, 1991). Such observations raise the possibility that a distinct PAF receptor may exist intracellularly.

3. Effects on airways.

a. AIRWAY SMOOTH MUSCLE. PAF has little direct effect on human airway smooth muscle contraction in vitro but may elicit constriction through the release of other mediators (Johnson *et al.,* 1992). PAF produces acute bronchoconstriction when inhaled by patients with asthma (Barnes *et al.,* 1989). PAF-induced bronchoconstriction is not inhibited by the H_1 receptor antagonist ketotifen (Chung *et al.,* 1988) or the Tx antagonist GR32191B (Stenton *et al.,* 1990b). However, PAF-induced bronchoconstriction can be inhibited by LT antagonists, including SKF 104353-Z (Spencer *et al.,* 1991) and ICI 204,219 (Kidney *et al.,* 1993), suggesting the involvement of LTD_4 in this response.

b. VESSELS. PAF has potent effects on vascular smooth muscle and elicits hypotension in several species (Barnes *et al.,* 1989). In the context of asthma, PAF is very potent in causing vascular engorgement and increased vascular permeability in the airways, leading to plasma exudation of protein-rich fluid into the airway lumen (O'Donnell and Barnett, 1987; Evans *et al.,* 1989). This may contribute to the acute airway obstruction elicited by PAF, because this effect is not totally reversed by the airway smooth muscle relaxant salbutamol (Diaz *et al.,* 1997). In animal studies, inhaled PAF is a potent inducer of airway plasma exudation (Lötvall *et al.,* 1991a), and this is mediated mainly via release of Tx (Tokuyama *et al.,* 1992). Inhalation of PAF by patients with mild asthma induces arterial blood gas abnormalities and ventilation/perfusion imbalances (Rodriguez-Roisin *et al.,* 1994; Felez *et al.,* 1994). This hypoxemia is not the result of the bronchoconstriction induced by PAF, because it cannot be fully inhibited by salbutamol (Roca *et al.,* 1995; Diaz *et al.,* 1997).

c. SECRETIONS. PAF stimulates fluid secretion from porcine isolated trachea via activation of PAF receptors and via a mechanism that does not depend on the release of acetylcholine, histamine, or cys-LTs (Steiger *et al.,* 1987). In feline airways, activation of PKC is involved (Larivee *et al.,* 1994). PAF also elicits mucus secretion from isolated human airways, which may depend in part on the generation of cys-LTs but is independent of acetylcholine release (Goswami *et al.,* 1989). PAF stimulates mucin secretion from cultured tracheal explants (Adler *et al.,* 1987).

d. NERVES. One possible explanation for the ability of PAF to induce increased responsiveness of the nose (Narita and Asakura, 1993) and airways (reviewed above) is that it functions via the activation of airway nerves. PAF-induced airway hyperresponsiveness in experimental animals has been demonstrated to be inhibited by capsaicin (Spina *et al.,* 1991; Perretti and Manzini, 1993), suggesting that PAF may have effects on the activation of sensory C-fibers in the airways. PAF upregulates the expression of H_1 receptor mRNA in trigeminal ganglia (Nakasaki *et al.,* 1998) and stimulates the transcription factor AP-1 in human neuroblastoma cells (Squinto *et al.,* 1989).

e. INFLAMMATORY CELLS. PAF is a potent activator of inflammatory cells. For example, PAF stimulates chemotaxis and adhesion of eosinophils and neutrophils in vitro (Kimani *et al.,* 1988; Kroegel *et al.,* 1988, 1991) In addition, PAF can act as a priming agent for eosinophils (Koenderman *et al.,* 1991; Blom *et al.,* 1992; Zoratti *et al.,* 1992). PAF-mediated priming of eosinophils is via different signaling pathways, compared with IL-5-induced priming, because it is not blocked by tyrosine kinase inhibitors (Van der Bruggen *et al.,* 1998). PAF enhances LTC_4 release from eosinophils from asthmatic patients but not from normal subjects (Shindo *et al.,* 1996). PAF induces greater activation of circulating eosinophils in vitro after allergen challenge of asthmatic patients, indicating an interaction between PAF and other priming factors, such as IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Evans *et al.,* 1996b). PAF also has a greater activating effect on neutrophils from asthmatic patients, compared with those from normal control subjects (Shindo *et al.,* 1997). In vivo, PAF elicits marked eosinophilic infiltration into lung tissue after both intravenous and aerosol administration to guinea pigs (Lellouch Tubiana *et al.,* 1988; Sanjar *et al.,* 1990) and rabbits (Coyle *et al.,* 1990). In both species, PAF-induced eosinophilic infiltration is reduced by selective platelet depletion with an antiplatelet antiserum, suggesting the involvement of platelets in eosinophil recruitment in vivo. In primates, single and multiple exposures to aerosolized PAF elicit an increase in the number of eosinophils and neutrophils in bronchoalveolar lavage fluid, accompanied by increased bronchial responsiveness to inhaled methacholine (Wegner *et al.,* 1992). Although inhalation of PAF has been reported to elicit bronchial hyperresponsiveness in humans (Cuss *et al.,* 1986; Kaye and Smith, 1990), this has not been universally shown (Spencer *et al.,* 1990; Lai *et al.,* 1990b), and it is associated with neutrophilic infiltration into the lungs (Wardlaw *et al.,* 1990). However, recent data from transgenic mice overexpressing a guinea pig PAF receptor have shown that such mice exhibit airway hyperresponsiveness to methacholine (Ishii *et al.,* 1997). In humans, intradermal administration of PAF to atopic subjects has been shown to induce eosinophilic infiltration (Henocq and Vargaftig, 1986).

4. Role in asthma.

a. RELEASE. Several groups have attempted to quantify the release of PAF in plasma or bronchoalveolar lavage fluid from asthmatic and allergic subjects, with conflicting results (Nakamura *et al.,* 1987; Miadonna *et al.,* 1989; Stenton *et al.,* 1990a; Tsukioka *et al.,* 1996). However, high levels of lyso-PAF were found in these studies and, because lyso-PAF is the precursor as well as the metabolite of PAF, this complicates the interpretation of these data. After segmental allergen challenge in asthmatic patients, high levels of lyso-PAF were correlated with increased acetylhydrolase and phospholipase A_2 activity (Chilton *et al.,* 1996). PAF has also been detected in the plasma of patients exhibiting a late asthmatic response (Chan Yeung *et al.,* 1991).

b. EFFECTS OF INHIBITORS. Despite considerable in vitro and in vivo data for humans suggesting that PAF is an important mediator of asthma, clinical studies with PAF receptor antagonists have been very disappointing. Apafant (WEB 2086) inhibited PAF-induced bronchoconstriction (Adamus *et al.,* 1990) and platelet responses to PAF (Hayes *et al.,* 1991) but had no significant effect on allergen-induced early or late responses or airway hyperresponsiveness (Freitag *et al.,* 1993). Furthermore, 12-week treatment of atopic asthmatics with apafant showed no clinical benefit in terms of lung function or

the use of rescue medication or inhaled corticosteroids (Spence *et al.,* 1994). Similarly, UK74505 abolishes PAF-induced bronchospasm (O'Connor *et al.,* 1994) but has no effect on allergen-induced early or late responses or on airway hyperresponsiveness (Kuitert *et al.,* 1993). UK80067, the racemate of UK74505, has no effect on adult asthmatics receiving this drug for 4 weeks (Kuitert *et al.,* 1995). Recent data suggested that 1-week treatment with the potent, long-acting, PAF receptor antagonist foropafant (SR27417A) produced a modest reduction in the magnitude of the allergen-induced late response, although there was no effect on the early response, the allergen-induced airway responsiveness, or base-line lung function (Evans *et al.,* 1997). Another PAF antagonist, Y24180, has also been shown to reduce airway responsiveness to inhaled methacholine in asthmatics (Hozawa *et al.,* 1995), although these data are at variance with findings from other studies (Hsieh, 1991; Evans *et al.,* 1997). Overall, these clinical data with PAF antagonists suggest that extracellular PAF plays only a small part in human allergic asthma, which is surprising, in view of its prominent role in animal models.

c. CONCLUSIONS. PAF is produced by many of the cells that are activated in asthmatic airways and has a profound effect on airway function, producing bronchoconstriction, inducing airway hyperresponsiveness, plasma exudation, and mucus hypersecretion, and recruiting and activating eosinophils. However, PAF antagonists have proved to be very disappointing for the treatment of asthma, producing minor or no effects, even during chronic treatment. This may be because PAF is not important in chronic asthma or because the antagonists used are not capable of blocking endogenously produced PAF, which acts locally in the airways almost as a "paracrine" mediator. A PAF synthase inhibitor would be particularly valuable for elucidation of the role of PAF and should also inhibit the production of intracellular PAF. It is possible that PAF may play a role in some patients with asthma and during exacerbations, but this has not yet been explored.

D. Other Lipid Mediators

1. Synthesis and metabolism. Several other lipid mediators, including hydroperoxyeicosatetraenoic acid (HPETEs), mono- and di-HETEs, and lipoxins (LXs), have been shown to have effects in the airways that are of potential relevance to asthma (Sigal and Nadel, 1991). Most of these substances are metabolic products of the 15-LO enzyme, which catalyzes the insertion of molecular oxygen at the carbon atom at position 15 in the arachidonic acid molecule (Samuelsson *et al.,* 1987). 15-LO has been demonstrated in human tracheal epithelium (Hunter *et al.,* 1985), eosinophils (Turk *et al.,* 1982), endothelial cells (Hopkins *et al.,* 1984), and monocytes (Conrad *et al.,* 1992). Furthermore, immunohistochemical studies have revealed that 15-LO is expressed in airway epithelium and eosinophils (Sigal *et al.,* 1992; Bradding *et al.,* 1995). LXs (LO interaction products), of which the most prevalent is LXA_4, are produced by interactions between 15-LO and 5-LO or between 12-LO and 5-LO.

2. Receptors. Little is known regarding receptors for 15-LO products, and it is not clear whether there are distinct receptors for these HETEs and HPETEs. Specific LXA_4 receptors have been identified in murine and human cells (Takano *et al.,* 1997; Fiore *et al.,* 1994).

3. Effects on airways. Both mono- and di-HETEs are chemotactic for neutrophils and eosinophils (Johnson *et al.,* 1985; Kirsch *et al.,* 1988; Morita *et al.,* 1990; Schwenk *et al.,* 1992). In addition, 15-HETE has been demonstrated to induce LTC_4 release from mastocytoma cells (Goetzl *et al.,* 1983) and mucus secretion from dog trachea (Johnson *et al.,* 1985). LXs have been demonstrated to contract airway smooth muscle (Dahlen *et al.,* 1987; Meini *et al.,* 1992) and to activate PKC (Hansson *et al.,* 1986). LXA_4 inhibits neutrophil and eosinophil activation by N-formyl-methionyl-leucyl-phenylalanine and PAF, respectively (Lee *et al.,* 1991; Soyombo *et al.,* 1994), and inhibits adhesion of leukocytes (Scalia *et al.,* 1997), suggesting that it has an anti-inflammatory role. LXA_4 also inhibits cholinergic neurotransmission in airways, an effect that may be mediated by release of NO (Tamaoki *et al.,* 1995).

The contribution of 15-LO metabolites of arachidonic acid to bronchial hyperresponsiveness is not clear. 15-HETE has been shown to reduce airway responsiveness but to prolong allergen-induced bronchospasm (Lai *et al.,* 1990a,b). Similarly, 15-HETE does not cause airway hyperresponsiveness in rabbits, despite causing infiltration of neutrophils into the airway (Riccio *et al.,* 1997). In contrast, 15-HPETE produces a sustained increase in airway responsiveness to inhaled histamine in rabbits, which is accompanied by neutrophilic infiltration (Riccio *et al.,* 1997). The airway hyperresponsiveness induced by inhaled 15-HPETE was significantly reduced by pretreatment with capsaicin and atropine, suggesting the involvement of airway cholinergic and peptidergic nerves (Riccio *et al.,* 1997).

4. Role in asthma. Immunoreactive LXA_4 has been detected in increased concentrations in bronchoalveolar lavage fluid from asthmatic patients (Lee *et al.,* 1990). Inhaled LXA_4 has little effect on airway function but antagonizes the bronchoconstricting effect of inhaled LTC_4 (Christie *et al.,* 1992), supporting the view that LXs may function as endogenous antagonists of cys-LTs (Lee, 1995). Stable LXA_4 analogues have anti-inflammatory effects and inhibit neutrophil chemotaxis and activation, suggesting that these endogenous substances are anti-inflammatory (Scalia *et al.,* 1997). 15-LO may therefore function as an anti-inflammatory regulator in asthma by controlling the formation of LXs in response to cys-LT formation in the airways. There is an increase in levels of mRNA for 15-LO in circulating leukocytes of asthmatic patients (Kuitert *et al.,* 1996) and increased

expression of 15-LO in epithelial cells of asthmatic patients (Bradding *et al.,* 1995). IL-4 selectively increases the expression of 15-LO in epithelial cells, and this may account for the increase in expression in asthma (Sigal *et al.,* 1993).

IV. Peptide Mediators

Several peptides, including bradykinin, tachykinins, CGRP, endothelins (ETs), and complement, are involved in asthma. They are usually cleaved from larger precursors and are released in an active form. They are subject to degradation by peptidases (such as NEP) both in the circulation and in the airways.

A. Bradykinin

Bradykinin has long been considered to be a mediator involved in asthma, since the first demonstration of bronchoconstriction in asthmatic patients after bradykinin inhalation. The development of potent and long-lasting bradykinin receptor antagonists has focused attention on the role of bradykinin and other kinins in the pathophysiological mechanisms of asthma, as well as on the potential uses of bradykinin antagonists in asthma therapy (Barnes, 1992b).

1. Synthesis and metabolism. Kinins are vasoactive peptides that are formed, during the inflammatory response, from the α_2-globulins high molecular weight (HMW) and low molecular weight (LMW) kininogens, by the action of kininogenases (Bhoola *et al.,* 1992). Kininogenases include plasma kallikrein and tissue kallikrein. HMW and LMW kininogens are produced from the same gene (containing 11 exons and 10 introns) as a consequence of alternative splicing (Nakanishi, 1987). Both kininogens are synthesized in the liver. HMW kininogen is present only in plasma, whereas LMW kininogen also occurs in tissues. Two kinins are formed in humans, i.e., the nonapeptide bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), which is generated from HMW kininogen, and the decapeptide lysyl-bradykinin (kallidin), which is generated from LMW kininogen. Kallidin is rapidly converted to bradykinin by the enzyme aminopeptidase-N (Proud and Kaplan, 1988). There is evidence for kinin activity in bronchoalveolar lavage fluid from asthmatic patients (Christiansen *et al.,* 1987, 1992), and it is likely that bradykinin is formed, by the action of plasma and tissue kallikreins, in plasma that has been exuded from the inflamed airways. The concentrations of kallikrein and kinins in bronchoalveolar lavage fluid increase after allergen challenge (Christiansen *et al.,* 1992). HMW kininogen is the preferred substrate for plasma kallikrein, which is generated from inactive prekallikrein by contact with certain negatively charged surfaces, including basement membrane components and proteoglycans, such as heparin released from mast cells. Tissue kallikreins are produced in glandular secretions and release kinins from both HMW and LMW kininogens. Tissue kallikrein has been localized immunocytochemically to serous cells in the submucosal glands of human airways (Proud and Vio, 1993). Serine proteases, such as α_1-antitrypsin, are effective inhibitors of kallikrein in the circulation, but in tissues kallikrein may remain activated for prolonged periods. Kallistatin is a kallikrein inhibitor that is present in some tissues, but its role in airways is not yet known (Chao *et al.,* 1996).

Other proteases that may be produced by inflammatory cells may also generate kinins from kininogens. Mast cell tryptase is a weak kininogenase in vitro under conditions of low pH, although it is unlikely that activity occurs to any significant extent in vivo (Proud *et al.,* 1988). There is also some evidence that neutrophils and platelets may release proteases with kininogen activity (Proud, 1991).

Bradykinin is subject to rapid enzymatic degradation and has a plasma half-life of <30 sec. Bradykinin is metabolized by several peptidases (collectively known as kininases), which may be present in asthmatic airways. Angiotensin-converting enzyme (ACE) may be important for degrading bradykinin in the circulation, because it is localized to endothelial cells, but it may also be present in airway tissue (Dusser *et al.,* 1988). ACE inhibitors, such as captopril and enalapril, potentiate both the bronchoconstriction and microvascular leakage produced by bradykinin (Ichinose and Barnes, 1990c; Lötvall *et al.,* 1991b), suggesting that this may be the mechanism of ACE inhibitor-induced cough. In guinea pigs, chronic administration of captopril causes spontaneous coughing, which is blocked by the bradykinin antagonist icatibant (Fox *et al.,* 1996).

NEP (EC 3.4.24.11) appears to be the most important enzyme for degradation of bradykinin in the airways. Phosphoramidon, which inhibits NEP, enhances the bronchoconstricting effect of bradykinin both in vitro (Frossard *et al.,* 1990) and in vivo (Ichinose and Barnes, 1990c; Lötvall *et al.,* 1991b) in animals. Because NEP is expressed in human airway epithelium (Baraniuk *et al.,* 1995), the shedding of airway epithelium in asthma may result in the enhanced airway responses to bradykinin seen in asthmatic patients.

A third enzyme, namely carboxypeptidase-N (kininase 1), may be important in degrading bradykinin in the circulation, but an inhibitor of this enzyme (DL-mercaptomethyl-3-guanidinoethylthiopropionic acid) does not have any effect on the bronchoconstriction response to bradykinin in vivo (Ichinose and Barnes, 1990c). Carboxypeptidase-N converts bradykinin to [des-Arg9]-bradykinin, which is selective for B_1 receptors (Regoli and Barabé, 1980). Aminopeptidase-M, which converts lysyl-bradykinin to bradykinin, is widely distributed, so that kallidin is rapidly converted to bradykinin. This enzyme is expressed in airway epithelial cells (Proud *et al.,* 1994).

2. Receptors. Bradykinin exerts several effects on the airways that are mediated by specific surface receptors. At

least two subtypes of bradykinin receptors are recognized, based on the rank order of potency of kinin agonists (Regoli and Barabé, 1980), as follows: B_1, [des-Arg10]-lysyl-bradykinin > [des-Arg9]-bradykinin = lysyl-bradykinin ≫ bradykinin; B_2, bradykinin = lysyl-bradykinin ≫ [des-Arg10]-lysyl-bradykinin > [des-Arg9]-bradykinin. B_1 receptors are selectively activated by lysyl-bradykinin (kallidin) and [des-Arg9]-bradykinin and are inducible by inflammatory signals. B_1 receptors are expressed in chronic inflammation induced by IL-1β and IL-6 in rats and may play an important role in hyperalgesia. The effects of bradykinin on airways are mediated by B_2 receptors, and there is no evidence for functional B_1 receptors in the airways. A B_3 receptor has also been proposed in airway smooth muscle of sheep (Farmer *et al.,* 1991), but there are doubts regarding its existence, because it has been defined with weak antagonists.

The B_2 receptor from animals and humans and a human B_1 receptor have been cloned (McEachern *et al.,* 1991; Hess *et al.,* 1992; Mencke *et al.,* 1995). Both have the typical seven-transmembrane segment structure common to all G protein-coupled receptors (McEachern *et al.,* 1991). Interestingly, [des-Arg10]-lysyl-bradykinin is much more potent than [des-Arg9]-bradykinin at the human B_1 receptor, suggesting that potential B_1 receptor responses in human tissues may be overlooked if [des-Arg9]-bradykinin is used as the only selective probe (Mencke *et al.,* 1995). Pharmacological studies suggest that there may be subtypes of B_2 receptors (Braas *et al.,* 1988; Hall, 1992), which may be more clearly defined using molecular probes. With low stringency probes, there is no evidence for additional types of bradykinin receptors in human cDNA libraries (Mencke *et al*., 1998).

The distribution of B_2 receptors has been mapped in human lung by autoradiography using [^{3}H]bradykinin (Mak and Barnes, 1991). There are high densities of binding sites in bronchial and pulmonary vessels, particularly on endothelial cells. Epithelial cells, airway smooth muscle (particularly in peripheral airways), submucosal glands, and nerves are also labeled, indicating that bradykinin may have diverse effects on airway function. A particularly high density of labeling is observed in the lamina propria immediately beneath the epithelium; it is not clear what cellular structures are labeled, but nerves and superficial blood vessels are the most likely structures.

3. Effects on airways. Bradykinin has many effects on airway functions; some are mediated by direct activation of B_2 receptors on target cells, and others are mediated indirectly via the release of other mediators or neurotransmitters.

a. AIRWAY SMOOTH MUSCLE. Inhaled bradykinin is a potent bronchoconstrictor in asthmatic patients but has little or no effect, even at high concentrations, in normal individuals, suggesting increased responsiveness of airway smooth muscle to bradykinin, as observed with other spasmogens (Fuller *et al.,* 1987b; Polosa and Holgate, 1990). In vitro, bradykinin is only a weak constrictor of proximal human airways, suggesting that its potent bronchoconstricting effect in asthmatic patients is mediated indirectly. However, bradykinin is more potent in constricting peripheral human airways (Molimard *et al.,* 1994; Hulsmann *et al.,* 1994b), partly via direct stimulation of B_2 receptors on airway smooth muscle cells and partly via the release of Tx. Bradykinin contracts airway smooth muscle in vitro, but in guinea pig airways in vitro bradykinin has weak and variable effects, which are influenced by the presence of airway epithelium and by the activity of local degrading enzymes. Bradykinin causes relaxation of intact guinea pig airways in vitro, but it constricts airways if the epithelium is mechanically removed (Frossard *et al.,* 1990; Bramley *et al.,* 1990). Bradykinin releases the bronchodilator PGE_2 from epithelial cells (Bramley *et al.,* 1990), and epithelium removal therefore reduces the functional antagonism, resulting in a bronchoconstricting effect of bradykinin. Furthermore, because NEP is strongly expressed on airway epithelial cells, epithelium removal may reduce bradykinin metabolism. A combination of indomethacin (to inhibit PGE_2 formation) and phosphoramidon (to inhibit NEP) mimics the effect of epithelium removal (Frossard *et al.,* 1990). The bronchoconstricting effect of bradykinin in ferrets in vitro and in guinea pigs in vivo is enhanced by the inhibition of both NEP (by phosphoramidon) and ACE (by captopril) (Dusser *et al.,* 1988; Ichinose and Barnes, 1990c). In small human bronchi in vitro, bradykinin may cause relaxation when the airway epithelium is intact but it consistently causes constriction after epithelium removal or addition of phosphoramidon (Hulsmann *et al.,* 1994b).

Intravenously administered bradykinin causes intense bronchoconstriction in guinea pigs, which is markedly inhibited by indomethacin, suggesting that a bronchoconstricting COX product (probably Tx) largely mediates this effect (Ichinose *et al.,* 1990a). The bronchoconstriction response to bradykinin instilled directly into the airways is not reduced by indomethacin, however, suggesting a different mechanism of bronchoconstriction after airway delivery of the mediator (Ichinose *et al.,* 1990a). In airway inflammation, it is likely that bradykinin would be formed at the airway surface from plasma kininogens exuded into the airway lumen from leaky superficial blood vessels. In human subjects, inhibition of COX by aspirin or flurbiprofen or treatment with a Tx receptor antagonist had no effect on the bronchoconstricting effect of inhaled bradykinin (Fuller *et al.,* 1987b; Polosa *et al.,* 1990; Rajakulasingam *et al.,* 1996), although in one study an inhibitory effect of inhaled lysine-aspirin was observed (Polosa *et al.,* 1997a). Similarly, antihistamines have no effect on bradykinin-induced bronchoconstriction, suggesting that mast cell mediator release is not involved (Polosa *et al.,* 1990).

The bronchoconstricting effect of bradykinin in guinea pigs is also modulated by NO, because pretreatment with aerosolized NOS inhibitors markedly potentiates the bronchoconstricting effect of bradykinin (administered intravenously or by inhalation) (Ricciardolo *et al.,* 1994). The source of NO is unclear but may be from airway epithelium, which expresses constitutive NOS (cNOS) and inducible NOS (iNOS) (Robbins *et al.,* 1994; Asano *et al.,* 1994). In asthmatic patients, inhalation of the NOS inhibitor N^G-monomethyl-L-arginine (L-NMMA) potentiates the bronchoconstricting action of bradykinin, suggesting that bradykinin releases NO in the airways to counteract the bronchoconstricting action of bradykinin (Ricciardolo *et al.,* 1996). Interestingly, this potentiating effect is not seen in patients with more severe asthma, possibly because of loss of the epithelial source of NO (Ricciardolo *et al.,* 1997).

In human airways, the bronchoconstricting effect of bradykinin is likely to be mediated by B_2 receptors, because icatibant blocks the bronchoconstriction response to bradykinin in vitro (Molimard *et al.,* 1994; Hulsmann *et al.,* 1994b) and the B_1-selective agonist [des-Arg9]-bradykinin has no effect on airway function in asthmatic patients (Polosa and Holgate, 1990). However, it is possible that B_1 receptors are induced in more severe asthma, and further studies with selective B_1 agonists are needed.

b. VESSELS. Bradykinin is a potent inducer of airway microvascular leakage and causes prolonged leakage at all airway levels. This is partly mediated by the release of PAF, because a PAF antagonist markedly inhibits the prolonged leakage (Rogers *et al.,* 1990). The immediate leakage response to bradykinin is partly mediated by the release of neuropeptides (probably SP) from airway sensory nerves. The effect of bradykinin on plasma exudation is partly reduced by pretreatment with neurokinin $(NK)_1$ receptor antagonists (Sakamoto *et al.,* 1993; Nakajima *et al.,* 1994). The effect of bradykinin on leakage is mediated by B_2 receptors (which have been localized to endothelial cells on postcapillary venules), because B_2 antagonists inhibit the leakage response (Ichinose and Barnes, 1990a; Sakamoto *et al.,* 1992). The microvascular leakage induced by bradykinin is enhanced by inhibition of both NEP and ACE (Lötvall *et al.,* 1991c).

Bradykinin is a potent vasodilator of bronchial vessels and causes an increase in airway blood flow (Parsons *et al.,* 1992a; Corfield *et al.,* 1991). This is consistent with the high density of bradykinin receptors on bronchial vessels (Mak and Barnes, 1991) and suggests that a major effect of bradykinin in asthma may involve hyperemia of the airways.

c. SECRETIONS. Bradykinin stimulates airway mucus secretion from human submucosal glands in vitro, and these effects are mediated by B_2 receptors (Nagaki *et al.,* 1996), presumably indicating a direct effect of bradykinin on submucosal glands. This is consistent with the demonstration of B_2 receptors on these glands by autoradiographic mapping (Mak and Barnes, 1991). Bradykinin also stimulates the release of mucus glycoproteins from human nasal mucosa in vitro (Baraniuk *et al.,* 1990). Bradykinin stimulates ion transport in airway epithelial cells, which is mediated by the release of PGs (Leikauf *et al.,* 1985). The effects of bradykinin on epithelial cells are mediated by B_2 receptors (Proud *et al.,* 1993). In animals, bradykinin also stimulates mucociliary clearance and ciliary beating via the release of PGs (Wong *et al.,* 1990). Inhaled bradykinin increases mucociliary clearance in normal humans, presumably reflecting the stimulatory effect of bradykinin on airway secretions (Polosa *et al.,* 1992a).

d. NERVES. Perhaps the most important property of bradykinin in airways is its ability to activate C-fiber nociceptive sensory nerve endings (Barnes, 1992b). Bradykinin is the mediator of inflammatory pain, and in the airways this may be manifested as cough and tightness of the chest, which are commonly observed in asthmatic patients after inhalation of bradykinin (Fuller *et al.,* 1987b). Bradykinin stimulates bronchial C-fibers in dogs. In guinea pigs, the bronchoconstriction response to instilled bradykinin is reduced by atropine and by capsaicin pretreatment, which depletes neuropeptides from sensory nerves, indicating that both a cholinergic reflex and release of neuropeptides from sensory nerves are involved (Ichinose *et al.,* 1990a). Indeed, a combination of atropine and capsaicin pretreatment largely abolishes the bronchoconstriction response to instilled bradykinin but has little effect on the bronchoconstriction response to intravenously administered bradykinin (which is largely inhibited by indomethacin) (Ichinose *et al.,* 1990a). Bradykinin also releases tachykinins from perfused guinea pig lung (Saria *et al.,* 1988) and rat trachea (Ray *et al.,* 1991). Bradykinin enhances the bronchoconstriction response to electrical field stimulation (mediated by release of endogenous tachykinins) in guinea pig bronchi in vitro (Miura *et al.,* 1992) and the NANC bronchoconstriction response to vagus nerve stimulation in vivo (Miura *et al.,* 1994). Tachykinin antagonists have an inhibitory effect on the bronchoconstriction and plasma exudation responses to bradykinin in guinea pigs, suggesting that release of tachykinins from sensory nerves is an important component of both responses (Sakamoto *et al.,* 1993; Nakajima *et al.,* 1994). The effect of bradykinin on airway sensory nerves is blocked by icatibant, indicating that B_2 receptors are involved in the release of neuropeptides from sensory nerves (Miura *et al.,* 1992). Although studies in human subjects are more limited, a nonselective tachykinin antagonist (FK-224) has been shown to reduce the bronchoconstriction response to inhaled bradykinin in asthmatic patients, suggesting that bradykinin may release tachykinins in asthmatic airways (Ichinose *et al.,* 1992); however, this was not confirmed in another study using the same antagonist (Schmidt *et al.,* 1996).

Single-fiber recordings from sensory nerves of guinea pig airways indicate that bradykinin is a potent activator of C-fibers and that this is a direct action, because it is not blocked by COX inhibition but is blocked by icatibant (Fox *et al.,* 1993). In guinea pigs treated with captopril, there is evidence for increased sensitization of C-fibers, which is blocked by icatibant, suggesting that bradykinin is responsible. Indeed, bradykinin sensitizes airway C-fibers to other neural activators (Fox *et al.,* 1996). However, bradykinin has no direct effect on the release of neurotransmitters from airway cholinergic nerves (Miura *et al.,* 1992).

In asthmatic patients, the bronchoconstriction response to bradykinin is reduced by anticholinergic pretreatment, indicating that a cholinergic reflex is involved (Fuller *et al.,* 1987b). Pretreatment with sodium cromoglycate and nedocromil sodium is very effective in inhibiting the airway response to bradykinin. This may indicate the involvement of C-fiber activation in asthmatic airways (Dixon and Barnes, 1989), because both drugs have been found to inhibit C-fibers in animals (Jackson *et al.,* 1989). This suggests that bradykinin may be an important mediator of cough and chest discomfort in asthma. Bradykinin induces cough in normal and asthmatic subjects (Choudry *et al.,* 1989) and has been implicated in ACE inhibitor-induced cough, which is observed for approximately 10% of patients receiving chronic therapy (Fuller, 1989). ACE inhibitor cough is reduced by COX inhibitors and Tx antagonists, suggesting that PGs (such as PGE_2 or $PGF_{2\alpha}$) may be involved (McEwan *et al.,* 1990; Malini *et al.,* 1997). Endogenous bradykinin may stimulate the release of these PGs in the larynx and trachea, leading to cough, although it is not clear why only some patients are affected.

e. INFLAMMATORY CELLS. Bradykinin has few reported direct effects on the recruitment or activation of inflammatory cells, although it may act indirectly through the release of mediators from structural cells. For example, bradykinin releases neutrophil and monocyte chemotactic factors from airway epithelial cells (Koyama *et al.,* 1995). Bradykinin activates alveolar macrophages from asthmatic patients to release mediators, including LTB_4, PAF, and other eosinophilic chemotactic factors (Sato *et al.,* 1996). In guinea pigs, a bradykinin antagonist inhibits allergen-induced eosinophilia, but whether bradykinin antagonists have such an effect in human airways has not been determined.

4. Role in asthma.

a. RELEASE. Although the role of bradykinin in asthma is still not clear, the development of potent, stable, B_2 receptor antagonists offers the possibility of soon clarifying the role of bradykinin in airway disease (Burch *et al.,* 1990). Bradykinin is generated in asthmatic airways by the action of various kininogenases (generated in the inflammatory response) on HMW kininogen present in the exuded plasma and on LMW kininogens secreted in the airways. Bradykinin has been detected in bronchoalveolar lavage fluid from asthmatic patients (Christiansen *et al.,* 1992). The degradation of bradykinin in the airways may be impaired when NEP is down-regulated in asthmatic airways or epithelial shedding occurs (Nadel, 1991). In experimental animals, aerosol exposure to IL-1β markedly increases the bronchoconstriction response to bradykinin (Tsukagoshi *et al.,* 1994a), and this may be the result of reduced expression of NEP in the airways (Tsukagoshi *et al.,* 1995).

b. RELEVANT EFFECTS. Asthmatic patients are hyperreactive to inhaled bradykinin; this is related to the degree of eosinophilic inflammation in the airways (Roisman *et al.,* 1996). Bradykinin has many effects on the airways that are relevant to asthma. Perhaps the most important property of bradykinin is its ability to activate nociceptive nerve fibers in the airway, because these may mediate the cough and chest tightness that are such characteristic symptoms of asthma. This effect of bradykinin may be enhanced by hyperesthesia of sensory nerves in the airways that have been sensitized by inflammatory mediators. Inhalation of bradykinin by asthmatic patients rather closely mimics an asthma attack; in addition to wheezing, patients experience chest tightness, coughing, and sometimes itching under the chin, which are common sensory manifestations during asthma exacerbation. Bradykinin is also a potent bronchoconstrictor in asthmatic patients, and after allergen challenge there is a disproportionate increase in responsiveness to bradykinin, compared with methacholine, which may not be maximal until several days after allergen challenge and may persist for several days (Berman *et al.,* 1995). This may be a reflection of airway sensory nerve hyperesthesia. In patients with perennial rhinitis, there is a marked increase in the response to topically applied bradykinin, with evidence of enhanced reflex effects (Baraniuk *et al.,* 1994).

c. EFFECTS OF INHIBITORS. The contribution of bradykinin to asthma can only be determined with the use of potent and specific bradykinin antagonists, which are now in clinical development. Such agents are predicted to be effective in symptom control, but it is not clear whether they might also have anti-inflammatory effects. One antagonist, [D-Arg^0,Hyp^3,D-Phe^7]-bradykinin (NPC567), was unable to inhibit the effect of bradykinin on nasal secretions, even when administered at the same time as bradykinin (Pongracic *et al.,* 1991), presumably because of rapid local metabolism. Icatibant (HOE 140, [D-Arg^0,Hyp^3,Thi^6,D-Tic^7,Oic^8]-bradykinin) is a selective B_2 receptor antagonist that not only is potent but also has a long duration of action in animals in vivo, because it is resistant to enzymatic degradation (Hock *et al.,* 1991; Wirth *et al.,* 1991). This antagonist is potent in inhibiting the bronchoconstriction and microvascular leakage responses to bradykinin (Wirth *et al.,* 1993; Sakamoto *et al.,* 1992) and the effect of bradykinin on airway sensory nerves (Miura *et al.,* 1992). Clinical studies with icatibant are limited, but there is some evidence

that nasal application reduces the nasal blockage induced by allergen in patients with allergic rhinitis (Austin *et al.,* 1994). In a clinical study of nebulized icatibant treatment of asthma, there was a small improvement in airway function tests after 4 weeks of treatment but no improvement in asthma symptoms (Akbary *et al.,* 1996). Recently, nonpeptide antagonists have been identified. WIN 64338 is a nonpeptide B_2 receptor antagonist that has been shown to block the bronchoconstricting action of bradykinin in airway smooth muscle in vitro (Scherrer *et al.,* 1995). More potent nonpeptide antagonists, such as FR167344, have been developed and have clinical potential (Inamura *et al.,* 1997). Although FR167344 is not very potent, it may lead to the future development of more potent nonpeptide drugs.

B. Tachykinins

Airway sensory nerves have the capacity to release neuropeptides, particularly the tachykinins SP and NKA, as well as CGRP, which may have proinflammatory effects in the airway. Because airway sensory nerves are activated in asthma, this has suggested that the release of sensory neuropeptides may contribute to the inflammatory response in asthma (Barnes, 1995a).

1. Synthesis and metabolism. SP and NKA, but not NKB, are localized to sensory nerves in the airways of several species (Barnes *et al.,* 1991; Joos *et al.,* 1994; Uddman *et al.,* 1997). SP-immunoreactive nerves are abundant in rodent airways but are sparse in human airways (Martling *et al.,* 1987; Laitinen *et al.,* 1992; Komatsu *et al.,* 1991). Rapid enzymatic degradation of SP in airways, and the fact that SP concentrations may decrease with age and possibly with cigarette smoking, could explain the difficulty in demonstrating this peptide in some studies. SP-immunoreactive nerves in the airway are found beneath and within the airway epithelium, around blood vessels, and, to a lesser extent, within airway smooth muscle. SP-immunoreactive nerves fibers also innervate parasympathetic ganglia, suggesting a sensory input that may modulate ganglionic transmission and thus result in local reflexes. SP in the airways is localized predominantly to capsaicin-sensitive unmyelinated nerves, but chronic administration of capsaicin only partially depletes the lung of tachykinins, indicating the presence of a population of capsaicin-resistant SP-immunoreactive nerves, as in the gastrointestinal tract (Dey *et al.,* 1991). Similar capsaicin denervation studies are not possible in human airways, but after extrinsic denervation during heart-lung transplantation there appears to be a loss of SP-immunoreactive nerves in the submucosa (Springall *et al.,* 1990). Tachykinins are derived from preprotachykinins (PPTs) that are expressed in nodose and jugular ganglia. There are three PPT genes; α-PPT codes for SP alone, β-PPT codes for SP and NKA, and γ-PPT codes for SP, NKA, and a novel, amino-terminally extended form of NKA termed NP-γ. Synthesis may be partly determined by local inflammation in the airways, because allergen exposure increases the expression of PPT mRNA in nodose ganglia of guinea pigs (Fischer *et al.,* 1996). There is some evidence that tachykinins may be synthesized in nonneuronal cells, such as macrophages. Human macrophages express α-PPT, and SP is released from these cells by capsaicin (Ho *et al.,* 1997). In rat alveolar macrophages, α-PPT mRNA and SP-like immunoreactivity are expressed in response to inflammatory stimuli, suggesting that this may result in increased SP release in inflammatory diseases (Killingsworth *et al.,* 1997).

Tachykinins are subject to degradation by at least two enzymes, ACE and NEP (Nadel, 1991). ACE is predominantly localized to vascular endothelial cells and therefore breaks down intravascular peptides. ACE inhibitors, such as captopril, enhance bronchoconstriction resulting from intravenous administration of SP (Shore *et al.,* 1988; Martins *et al.,* 1990) but not inhalation of SP (Lötvall *et al.,* 1990b). NKA is not a good substrate for ACE, however. NEP appears to be the most important enzyme for the breakdown of tachykinins in tissues. Inhibition of NEP by phosphoramidon or thiorphan markedly potentiates bronchoconstriction in vitro in animal airways (Sekizawa *et al.,* 1987) and human airways (Black *et al.,* 1988) and after inhalation in vivo (Lötvall *et al.,* 1990b). NEP inhibition also potentiates mucus secretion in response to tachykinins in human airways (Rogers *et al.,* 1989). NEP inhibition enhances excitatory NANC and capsaicin-induced bronchoconstriction, resulting from the release of tachykinins from airway sensory nerves (Frossard *et al.,* 1989; Djokic *et al.,* 1989). The activity of NEP in the airways appears to be an important factor determining the effects of tachykinins; any factors that inhibit the enzyme or its expression may be associated with increased effects of exogenously applied or endogenously released tachykinins. Several of the stimuli known to induce bronchoconstriction responses in asthmatic patients have been found to reduce the activity of airway NEP (Nadel, 1991).

2. Receptors. At least three subtypes of tachykinin receptors have been characterized pharmacologically by the rank order of potency of agonists, by the development of selective antagonists, and by molecular cloning (Nakanishi, 1991). SP acts preferentially at NK_1 receptors, NKA at NK_2 receptors, and NKB at NK_3 receptors. Tachykinin receptors are differentially expressed and are also subject to differential regulation, for example by inflammatory stimuli. Tachykinins are typical G protein-coupled receptors and lead to increased PI hydrolysis, with an increase in the release of intracellular Ca^{2+}, IP_3, and diacylglycerol. Tachykinin receptors in the airways have been mapped using autoradiographic techniques and labeled tachykinins (Carstairs and Barnes, 1986; Walsh *et al.,* 1994; Strigas and Burcher, 1996; Miyayasu *et al.,* 1993; Zhang *et al.,* 1995). NK_1 receptors are localized to bronchial vessels, epithelial cells, and

submucosal glands, whereas NK_2 receptors are predominantly localized to airway smooth muscle.

3. Effects on airways. Tachykinins have many different effects on the airways that may be relevant to asthma, and these effects are mediated by NK_1 and NK_2 receptors. There is little evidence for the involvement of NK_3 receptors.

a. AIRWAY SMOOTH MUSCLE. Tachykinins constrict human airway smooth muscle in vitro via NK_2 receptors (Naline *et al.,* 1989; Advenier *et al.,* 1992b; Sheldrick *et al.,* 1995). The contractile response to NKA is significantly greater in smaller human bronchi than in more proximal airways, indicating that tachykinins may have a more important constricting effect in peripheral airways (Frossard and Barnes, 1991), whereas cholinergic constriction tends to be more pronounced in proximal airways. This is consistent with the autoradiographic distribution of tachykinin receptors, showing distribution to small and large airways (Carstairs and Barnes, 1986). NP-γ is also a potent constrictor of human airways and acts via NK_2 receptors (Burcher *et al.,* 1991). In vivo, SP does not cause bronchoconstriction or cough when administered either by intravenous infusion (Fuller *et al.,* 1987c; Evans *et al.,* 1988) or by inhalation (Fuller *et al.,* 1987c; Joos *et al.,* 1987), whereas NKA causes bronchoconstriction in asthmatic subjects after both intravenous administration (Evans *et al.,* 1988) and inhalation (Joos *et al.,* 1987). Inhalation of SP increases airway responsiveness to methacholine in asthmatic subjects, an effect that has been ascribed to airway edema (Cheung *et al.,* 1995). Mechanical removal of airway epithelium potentiates the bronchoconstriction response to tachykinins (Frossard *et al.,* 1989; Devillier *et al.,* 1988), largely because epithelial NEP is removed.

b. VESSELS. Tachykinins have potent effects on airway blood flow. Indeed, the effects of tachykinins on airway blood flow may be the most important physiological and pathophysiological effects of tachykinins in airways. In canine and porcine trachea, both SP and NKA cause marked increases in blood flow (Salonen *et al.,* 1988; Matran *et al.,* 1989). Tachykinins also dilate canine bronchial vessels in vitro, probably via an endothelium-dependent mechanism (McCormack *et al.,* 1989b). Tachykinins also regulate bronchial blood flow in pigs; stimulation of the vagus nerve causes vasodilation mediated by the release of sensory neuropeptides, and it is likely that CGRP as well as tachykinins are involved (Matran *et al.,* 1989).

Stimulation of the vagus nerve in rodents causes microvascular leakage, which is prevented by prior treatment with capsaicin or a tachykinin antagonist, indicating that release of tachykinins from sensory nerves mediates this effect. Among the tachykinins, SP is most potent at causing leakage in guinea pig airways (Rogers *et al.,* 1988), and NK_1 receptors have been localized to postcapillary venules in the airway submucosa (Sertl *et al.,* 1988). Inhaled SP also causes microvascular leakage in guinea pigs, and its effect on the microvasculature is more marked than its effect on airway smooth muscle (Lötvall *et al.,* 1990a). It is difficult to measure airway microvascular leakage in human airways, but SP causes weals in human skin when injected intradermally, indicating its capacity to cause microvascular leakage in human postcapillary venules; NKA is less potent, indicating that an NK_1 receptor mediates this effect (Fuller *et al.,* 1987a).

c. SECRETIONS. In vitro, SP stimulates mucus secretion from submucosal glands (mediated by NK_1 receptors) in ferret and human airways (Rogers *et al.,* 1989; Ramnarine *et al.,* 1994; Meini *et al.,* 1993) and is a potent stimulant of goblet cell secretion in guinea pig airways (Kuo *et al.,* 1990). Indeed, SP is likely to mediate the increases in goblet cell discharge after vagus nerve stimulation and exposure to cigarette smoke (Tokuyama *et al.,* 1990; Kuo *et al.,* 1992a).

d. NERVES. In guinea pig trachea, tachykinins also potentiate cholinergic neurotransmission at postganglionic nerve terminals, and an NK_2 receptor appears to be involved (Hall *et al.,* 1989). There is also potentiation at the ganglionic level (Undem *et al.,* 1991; Watson *et al.,* 1993), which appears to be mediated by a NK_1 receptor (Watson *et al.,* 1993). There is evidence that NK_3 receptors may also be involved (Myers and Undem, 1993). Endogenous tachykinins may also facilitate cholinergic neurotransmission, because capsaicin pretreatment results in a significant reduction in cholinergic neural responses both in vitro and in vivo (Martling *et al.,* 1984; Stretton *et al.,* 1992). However, in human airways there is no evidence for a facilitatory effect on cholinergic neurotransmission (Belvisi *et al.,* 1994), although such an effect has been reported in the presence of potassium channel blockers (Black *et al.,* 1990). In conscious guinea pigs, very low concentrations of inhaled SP are reported to cause cough, and this effect is potentiated by NEP inhibition (Kohrogi *et al.,* 1988). Citric acid-induced cough and airway hyperresponsiveness are blocked by a nonpeptide NK_2 receptor antagonist (SR 48968), suggesting the involvement of NK_2 receptors, although these may be centrally located (Advenier *et al.,* 1992a; Girard *et al.,* 1996).

e. INFLAMMATORY CELLS. Tachykinins may also interact with inflammatory and immune cells (Daniele *et al.,* 1992), although whether this is of pathophysiological significance remains to be determined. SP degranulates certain types of mast cells, such as those in human skin (although this effect is not mediated by a tachykinin receptor) (Lowman *et al.,* 1988); however there is no evidence that tachykinins degranulate lung mast cells (Ali *et al.,* 1986). SP has a degranulating effect on eosinophils (Kroegel *et al.,* 1990), but this is not mediated by a tachykinin receptor. At lower concentrations, tachykinins have been reported to enhance eosinophil chemotaxis (Numao and Agrawal, 1992). Tachykinins may activate alveolar macrophages (Brunelleschi *et al.,* 1990)

and monocytes to release inflammatory cytokines, such as IL-6 (Lötz *et al.,* 1988). Topical application of SP to human nasal mucosa results in increased expression of several cytokines, suggesting that SP may have important chronic immunological effects (Okamoto *et al.,* 1995). Tachykinins and vagus nerve stimulation also cause transient vascular adhesion of neutrophils in the airway circulation (Umeno *et al.,* 1989) and in human skin (Smith *et al.,* 1993).

SP stimulates proliferation of blood vessels (angiogenesis) (Fan *et al.,* 1993) and may therefore be involved in the new vessel formation that is found in asthmatic airways. SP and NKA also stimulate the proliferation and chemotaxis of human lung fibroblasts, suggesting that tachykinins may contribute to the fibrotic process in chronic asthma (Harrison *et al.,* 1995). These effects appear to be mediated by both NK_1 and NK_2 receptors.

4. Role in asthma. In rodents, there is now considerable evidence for neurogenic inflammation in airways resulting from antidromic release of neuropeptides from nociceptive nerves or C-fibers, via an axon reflex, and this process may contribute to the inflammatory response in asthma (Barnes, 1986).

a. RELEASE. Quantitative studies in humans indicate that SP-immunoreactive fibers constitute only 1% of the total number of intraepithelial fibers, whereas in guinea pigs they comprise 60% of the fibers (Bowden and Gibbins, 1992). A striking increase in SP-immunoreactive nerves was reported in the airways of patients with fatal asthma (Ollerenshaw *et al.,* 1991), but this finding has not been confirmed in biopsies from patients with milder asthma (Howarth *et al.,* 1995) and there is no increase in the SP content of lungs from asthmatics (Lilly *et al.,* 1995). After nasal challenge with allergen, an increase in the SP content in nasal lavage fluid has been reported (Mosiman *et al.,* 1993). Elevated concentrations of SP in bronchoalveolar lavage fluid from patients with asthma have been reported, with an additional increase after allergen challenge (Nieber *et al.,* 1992), suggesting that there may be an increase in the SP content in the airways of asthmatic patients. Similarly, SP has been detected in the sputum of asthmatic patients after inhalation of hypertonic saline solution (Tomaki *et al.,* 1995). Allergen challenge is associated with a doubling of the number of PPT-A mRNA-positive neurons in nodose ganglia of guinea pigs and an increase in SP and CGRP immunoreactivity in the lungs (Fischer *et al.,* 1996).

b. RELEVANCE IN ASTHMA. Sensory nerves may be activated in airway disease. In asthmatic airways the epithelium is often shed, thereby exposing sensory nerve endings. Sensory nerves in asthmatic airways may be "hyperalgesic" as a result of exposure to inflammatory mediators such as PGs and certain cytokines (such as IL-1β, TNF-α, and nerve growth factor) and may then be activated more readily by other mediators, such as kinins. In animals, capsaicin has been used as a tool to explore the release of sensory neuropeptides. In humans, capsaicin inhalation causes cough and transient bronchoconstriction, which is inhibited by cholinergic blockade and is probably attributable to a laryngeal reflex (Fuller *et al.,* 1985; Midgren *et al.,* 1992). This suggests that neuropeptide release does not occur in human airways, although it is possible that insufficient capsaicin reaches the lower respiratory tract because the dose is limited by coughing. There is no evidence that capsaicin induces a greater degree of bronchoconstriction in patients with asthma than in normal individuals (Fuller *et al.,* 1985).

In contrast to studies in rodents, the NEP inhibitor acetorphan has no effect on base-line airway caliber or on bronchoconstriction induced by a "neurogenic" trigger (sodium metabisulfite) in human subjects (Nichol *et al.,* 1992). The lack of effect could be the result of inadequate inhibition of NEP in the airways, particularly at the level of the epithelium. Nebulized thiorphan has been shown to potentiate the bronchoconstriction response to inhaled NKA in normal and asthmatic subjects (Cheung *et al.,* 1992a,b), but there is no effect on base-line lung function in asthmatic patients (Cheung *et al.,* 1992b), indicating that there is unlikely to be basal release of tachykinins. It is possible that NEP may become dysfunctional after viral infections or exposure to oxidants, thus contributing to asthma exacerbations (Nadel, 1991).

There is evidence that NK_1 receptor gene expression might be increased in the lungs of asthmatic patients (Adcock *et al.,* 1993). This might be the result of increased transcription in response to activation of transcription factors, such as AP-1, which are activated in human lung by cytokines such as TNF-α. Expression of NK_2 receptors has also been described in asthma (Bai and Bramley, 1993).

c. EFFECTS OF INHIBITORS. There have recently been several studies of tachykinin antagonists in asthma. The relatively weak, nonselective, tachykinin antagonist FK-224 had an inhibitory effect on bradykinin-induced bronchoconstriction in asthma (Ichinose *et al.,* 1992), although this finding was not confirmed in another study (Schmidt *et al.,* 1996). A more potent NK_1 receptor antagonist, FK-888, reduced the duration of exercise-induced asthma but had no effect on maximal bronchoconstriction, suggesting an effect on blood vessels rather than airway smooth muscle (Ichinose *et al.,* 1996). However, another potent NK_1 receptor antagonist, CP 99,994, had no effect on hypertonic saline solution-induced bronchoconstriction or on cough (Fahy *et al.,* 1995).

Apart from tachykinin receptor antagonists, neurogenic inflammation may be modulated by either preventing the activation of sensory nerves or preventing the release of neuropeptides. Many drugs act on prejunctional receptors to inhibit the release of neuropeptides (Barnes *et al.,* 1990). Opioids are the most effective inhibitors, but an inhaled, peripherally acting, μ-opioid

agonist (the pentapeptide BW443C) was found to be ineffective in inhibiting metabisulfite-induced bronchoconstriction, which is believed to occur via neural mechanisms (O'Connor *et al.,* 1991).

d. CONCLUSIONS. Tachykinins are increased in the secretions of asthmatic patients and may be produced by sensory nerves, although there is increasing evidence that inflammatory cells, such as macrophages, may release SP. Tachykinins are potent bronchoconstrictors (acting via NK_2 receptors) and stimulate mucus secretion, plasma exudation, neural activation, and structural changes (via NK_1 receptors). However, the negative results obtained with tachykinin antagonists in asthma suggest that neurogenic inflammation is unlikely to play a major role, at least in mild asthma. It is possible that sensory neuropeptides play a role in more severe asthma, and further studies are needed.

C. Calcitonin Gene-Related Peptide

1. Synthesis and metabolism. CGRP-immunoreactive nerves are abundant in the respiratory tract of several species, and CGRP is stored and localized with SP in afferent nerves. CGRP has been extracted from and is localized to human airways (Palmer *et al.,* 1987; Komatsu *et al.,* 1991). CGRP is found in trigeminal, nodosejugular, and dorsal root ganglia and has also been detected in neuroendocrine cells of the lower airways (Uddman *et al.,* 1997).

The metabolism of CGRP is less clear, although NEP inhibitors increase some of the effects of CGRP in the airways (Katayama *et al.,* 1991). Interestingly, metabolism of CGRP by NEP appears to liberate a peptide fragment that has eosinophil chemotactic activity (Davies *et al.,* 1992).

2. Receptors. CGRP acts on specific receptors that are coupled (via G_s) to adenylyl cyclase, resulting in an increase in intracellular cyclic AMP concentrations. Subtypes of CGRP receptors have been proposed, based on the selectivity of different CGRP analogues and the related peptide amylin (Poyner, 1992). CGRP receptors have been mapped autoradiographically in human airways and are predominantly located in bronchial vascular smooth muscle, rather than airway epithelium (Mak and Barnes, 1988).

3. Effects on airways.

a. AIRWAY SMOOTH MUSCLE. CGRP causes constriction of human bronchi in vitro (Palmer *et al.,* 1987). This is surprising, because CGRP increases cyclic AMP levels. There are few, if any, CGRP receptors in airway smooth muscle in human or guinea pig airways, and this suggests that the paradoxical bronchoconstriction response reported in human airways may be mediated indirectly. In guinea pig airways, CGRP has no consistent effect on tone (Martling *et al.,* 1988). The variable effects of CGRP on airways may be explained by the fact that CGRP may release other mediators that have effects on tone. CGRP may release both NO and ET in airways, so that its effects would depend on the balance between these bronchodilating and bronchoconstricting mediators (Ninomiya *et al.,* 1996).

b. VESSELS. CGRP is a potent vasodilator that has long-lasting effects. CGRP is an effective dilator of human pulmonary vessels in vitro and acts directly on receptors in vascular smooth muscle (McCormack *et al.,* 1989a). It also potently dilates bronchial vessels in vitro (McCormack *et al.,* 1989a) and produces a marked and long-lasting increase in airway blood flow in vivo in anesthetized dogs (Salonen *et al.,* 1988) and conscious sheep (Parsons *et al.,* 1992a). It is possible that CGRP may be the predominant mediator of arterial vasodilation and increased blood flow in response to sensory nerve stimulation in the bronchi (Matran *et al.,* 1989). There are high densities of CGRP receptors in bronchial vessels in human airways (Mak and Barnes, 1988), suggesting that CGRP may be an important mediator of airway hyperemia in asthma. CGRP has no direct effect on airway microvascular leakage (Rogers *et al.,* 1988). CGRP may potentiate the leakage produced by SP by increasing blood delivery to the sites of plasma extravasation in the postcapillary venules; this has been seen in rat airways (Brokaw and White, 1992). This does not occur in guinea pig airways when CGRP and SP are coadministered, possibly because blood flow in the airways is already high (Rogers *et al.,* 1988).

c. SECRETIONS. CGRP has a weak inhibitory effect on cholinergically stimulated mucus secretion in ferret trachea (Webber *et al.,* 1991) and on goblet cell discharge in guinea pig airways (Kuo *et al.,* 1990), whereas it increases secretion in feline submucosal glands (Nagaki *et al.,* 1994). There are low densities of CGRP receptors on mucus secretory cells (Mak and Barnes, 1988), but this finding does not eliminate the possibility that CGRP might increase mucus secretion in vivo by increasing blood flow to submucosal glands.

d. INFLAMMATORY CELLS. CGRP injection into human skin causes a persistent flare, but biopsies have revealed an infiltration of eosinophils (Pietrowski and Foreman, 1986). CGRP itself does not appear to be chemotactic for eosinophils, but proteolytic fragments of the peptide are active (Davies *et al.,* 1992), suggesting that CGRP released into the tissues may lead to eosinophilic infiltration. CGRP inhalation induces eosinophilic inflammation in rat lungs (Bellibas, 1996). In contrast, CGRP inhibits macrophage secretion and the capacity of macrophages to activate T lymphocytes (Nong *et al.,* 1989), suggesting potential anti-inflammatory actions. CGRP also induces proliferation of guinea pig airway epithelial cells and may therefore be involved in healing the airway after epithelial shedding in asthma (White *et al.,* 1993).

4. Role in asthma. To date there is little evidence for the involvement of CGRP in asthma. Its most prominent action is prolonged vasodilation, so it may contribute to the hyperemia of asthmatic airways. There are currently

no antagonists that are suitable for clinical use, so it is difficult to evaluate the role of CGRP in asthma

D. Endothelins

ETs are potent constrictor peptides that were originally described as vasoconstrictors released from endothelial cells. There is now considerable circumstantial evidence that they are involved in the pathophysiological mechanisms of asthma (Barnes, 1994b; Hay *et al.,* 1996).

1. Synthesis and metabolism. There are three ET peptides, and each is encoded by a distinct gene (Inoue *et al.,* 1989), which codes for the precursor peptide. Prepro-ET-1 is cleaved to a 38-amino acid intermediate form termed big ET-1 or pro-ET-1. Pro-ET-1 is rapidly cleaved by a specific enzyme, termed ET-converting enzyme (ECE), to form mature ET-1. ECE is a neutral metalloendopeptidase and is inhibited by phosphoramidon (Ikegawa *et al.,* 1990). Mast cell chymase may also cleave pro-ET-1 (Wypij *et al.,* 1992). The human prepro-ET-1 gene is on chromosome 6, and its upstream regulatory region reveals multiple regulatory elements, indicating that several factors may regulate its expression (Masaki *et al.,* 1992). Several proinflammatory cytokines, including transforming growth factor (TGF)-β, TNF-α, and IL-1β, may increase expression of ET-1. Less is known regarding the synthetic pathways and regulation of ET-2 and ET-3.

ETs may be stored within cells but are predominantly synthesized upon cell activation; secretion of ETs is therefore largely regulated at the level of peptide synthesis. Although ET-1 was first described in endothelial cells, it is now apparent that ETs can be synthesized by many different cell types, including several types of airway cells. ET-3 is relatively abundant in neuronal tissues and may be a neuronal ET form. ET-like immunoreactivity is localized to airway epithelium in human airways, with intense staining in goblet and Clara cells but only intermittent staining in ciliated epithelial cells (Giaid *et al.,* 1991). Specific antibodies have localized ET-1, pro-ET-1, ET-3, and pro-ET-3 to airway epithelial cells and submucosal glands in human lung (Marciniak *et al.,* 1992). ECE has been reported in bovine lung membranes (Kundu and Wilson, 1992), and guinea pig lung is reported to synthesize and degrade ET-1 (Noguchi *et al.,* 1991). The presence of pro-ETs and mRNA for prepro-ETs in lung suggests that ETs are synthesized locally within lung cells. Furthermore, ET-1 is detectable in cultured human epithelial cells (Black *et al.,* 1989b; Mattoli *et al.,* 1990). ET-1 synthesis and release from epithelial cells are stimulated by endotoxin and by several proinflammatory cytokines (IL-1β, TNF-α, and IL-6), which may be released from macrophages (Endo *et al.,* 1992). Human alveolar macrophages have also been identified as a source of ETs (Ehrenreich *et al.,* 1990), and these cells may be activated in asthmatic patients by exposure to allergens via low affinity IgE receptors.

ETs are metabolized by NEP, which is localized in several cell types in airways, especially airway epithelium. Inhibition of NEP with phosphoramidon increases the potency of ETs in guinea pigs in vivo (Boichot *et al.,* 1991) and in human airways in vitro (Candenas *et al.,* 1992).

2. Receptors. Pharmacological responses to ETs are mediated by at least two receptor subtypes. Two distinct receptors, with structures typical of G protein-coupled receptors, have been cloned; they exhibit approximately 60% homology (Masaki *et al.,* 1992). For the ET_A receptor, the rank order of potency is ET-1 > ET-2 $\gg$ ET-3 and the binding affinity for ET-1 is approximately 100 times greater than that for ET-3. ET_B receptors show similar affinities for all three ETs and for the related sarafotoxins. The distinction between ET_A and ET_B receptors has been confirmed with the development of selective agonists and antagonists. Although the existence of a third ET receptor, which is selective for ET-3 (ET_C receptor), has been proposed (Masaki *et al.,* 1992), there is little conclusive evidence for this in human tissues. Radioligand binding studies and in situ hybridization studies with receptor cDNA probes have demonstrated that ET receptors are widely distributed, in keeping with the multiple actions of these peptides. ET_A and ET_B receptors are expressed in lung and are differentially distributed (Nakamichi *et al.,* 1992). Selective ET_A and ET_B agonists and antagonists have greatly aided the study of receptor subtype expression. BQ-123, FR-139317, and PD 145065 are selective ET_A receptor antagonists, whereas IRL 1038 is a selective antagonist of ET_B receptors.

Autoradiographic studies with ^{125}I-ET-1 and selective antagonists have shown a widespread distribution of ET_A and ET_B receptors in human airways, with a predominance of ET_B receptors in airway smooth muscle (Knott *et al.,* 1995). There is no difference in receptor distribution in airways from asthmatic patients, compared with airways from normal subjects (Goldie *et al.,* 1995).

3. Effects on airways.

a. AIRWAY SMOOTH MUSCLE. ET-1 and ET-2 are potent constrictors of human airway smooth muscle in vitro, being even more potent than LTD_4 (Advenier *et al.,* 1990; Henry *et al.,* 1990; McKay *et al.,* 1991b; Takahashi *et al.,* 1997; Goldie *et al.,* 1995). The contractile response is slow in onset and sustained, and ET-1 appears to cause a maximal contractile response. The contractile response in human airways is unaffected by calcium antagonists or (in contrast to other species) COX inhibitors or LT antagonists (McKay *et al.,* 1991a; Nally *et al.,* 1994), suggesting a direct effect on airway smooth muscle. This is consistent with the demonstration of ET binding sites on human airway smooth muscle, using autoradiography (Henry *et al.,* 1990; McKay *et al.,* 1991b; Brink *et al.,* 1991; Goldie *et al.,* 1995; Knott *et al.,* 1995). ET-1 may produce a prolonged contractile re-

sponse in human airway smooth muscle by activating PKC, because the PKC inhibitor staurosporine reduces the constricting effect of ET-1 (McKay *et al.,* 1996). ET-3 is less potent that ET-1 or ET-2 (Advenier *et al.,* 1990; Hay *et al.,* 1993), but the potency differences are complicated by differential metabolism. Mechanical removal of airway epithelium potentiates the constricting effects of ETs, but the effect is greater for ET-3 than for ET-1 (Candenas *et al.,* 1992; McKay *et al.,* 1992). After epithelium removal or phosphoramidon treatment, the potencies of ET-1, ET-2, and ET-3 are similar, suggesting that any differences in previous studies were the result of more rapid degradation of ET-3 by epithelial NEP. ET-3-mediated contraction of human airways is partly reduced by COX inhibition (Nally *et al.,* 1994).

The ET_A antagonists BQ-123, FR-139317, and PD 145065 have no inhibitory effect on ET-induced constriction, suggesting that ET_B receptors mediate the direct constriction response, and this is supported by the constriction response to the ET_B-selective agonists BQ-3020 and IRL1620 (Hay *et al.,* 1993; Takahashi *et al.,* 1997). Asthmatic airways show a similar, or even reduced, response to ET_B-selective agonists, compared with normal airways (Goldie *et al.,* 1995). Interestingly, the release of prostanoids (predominantly PGD_2 and PGE_2) induced by ET-1 in human airways appears to be mediated by an ET_A receptor, because this is effectively inhibited by BQ-123 (Hay *et al.,* 1993). Inhaled ET-1 is a potent bronchoconstrictor (approximately 100-fold more potent than methacholine) in asthmatic patients and causes a bronchoconstriction response that lasts for >1 h, whereas ET-1 has no effect in normal subjects (Chalmers *et al.,* 1997a).

ET-1 increases proliferation of rabbit and sheep cultured airway smooth muscle cells (Noveral *et al.,* 1992; Glassberg *et al.,* 1994; Carratu *et al.,* 1997), and this appears to be via stimulation of the extracellular signal-regulated kinase/MAP kinase pathway (Whelchel *et al.,* 1997). ET-1 alone has no effect on cultured human airway smooth muscle cells but markedly amplifies the proliferative effects of growth factors, such as epidermal growth factor (EGF); this is mediated by an ET_A receptor (Panettieri *et al.,* 1996).

b. VESSELS. ET-1 constricts human bronchial arteries in vitro (McKay *et al.,* 1991a), but its effects on airway microvascular leakage are conflicting. ET-1 causes an increase in plasma extravasation in rat trachea (Sirois *et al.,* 1992) and this response is dependent on leukocytes (Helset *et al.,* 1993), whereas ET-1 is without effect on plasma extravasation in guinea pigs (Macquin-Mavier *et al.,* 1989). This may reflect relative vasoconstricting effects on precapillary arterioles versus direct effects on endothelial cells of postcapillary venules.

c. SECRETION. ET-1, but not ET-2 or ET-3, stimulates mucus glycoprotein secretion from feline airway submucosal glands via a direct mechanism that involves calcium ion influx, suggesting that ET_A receptors are involved (Shimura *et al.,* 1992). ET-1 also stimulates ion transport in cultured airway epithelial cells (Wong *et al.,* 1990).

d. NERVES. ETs bind to parasympathetic ganglia and nerves in rat and rabbit airways (Turner *et al.,* 1989; Power *et al.,* 1989; McKay *et al.,* 1993), suggesting that ET-3 may have an effect on cholinergic neurotransmission. ET-3 enhances neurotransmission in postganglionic cholinergic nerves in rabbit airways via a direct effect on prejunctional receptors on postganglionic cholinergic nerves (McKay *et al.,* 1993). This suggests that ETs may potentiate cholinergic reflex bronchoconstriction and this effect is mediated by an ET_B receptor. The ET_B-selective agonist sarafotoxin S6C enhances cholinergic nerve-induced contraction of human airways in vitro, indicating the presence of ET_B receptors on cholinergic nerves as well as airway smooth muscle (Fernandes *et al.,* 1996).

e. INFLAMMATORY CELLS. It is not yet certain whether ETs have inflammatory effects in the airways. Intravenously administered or inhaled ET-1 has no effect on inflammatory cell influx in guinea pigs (Macquin-Mavier *et al.,* 1989), and there is no increase in airway responsiveness to other spasmogens (Lagente *et al.,* 1989). ETs may increase the release of inflammatory mediators from a variety of cells. ET-1 increases the release of lipid mediators from cultured human nasal mucosa (Wu *et al.,* 1992) and increases superoxide formation and TNF-α release in alveolar macrophages (Haller *et al.,* 1991; Chanez *et al.,* 1996). ET-1 also releases histamine from guinea pig lung, but not peritoneal, mast cells (Uchida *et al.,* 1992). In a cultured human epithelial cell line, ET-1 induces the release of the cytokines IL-6, IL-8, and GM-CSF (Mullol *et al.,* 1996).

ET-1 potently stimulates collagen secretion from pulmonary fibroblasts (Peacock *et al.,* 1992) and may therefore be involved in the increased collagen formation observed in asthmatic airways. ET-1 is reported to increase fibronectin gene expression and protein release in human airway epithelial cells (Marini *et al.,* 1996).

4. Role in asthma.

a. RELEASE. There is increased formation of ETs in asthma. Elevated concentrations of ET-1 have been detected in bronchoalveolar lavage fluid from asthmatic patients (Mattoli *et al.,* 1991; Sofia *et al.,* 1993; Redington *et al.,* 1995), and these are reduced after treatment with steroids (Vittori *et al.,* 1992). ET-1 is present in induced sputum, but the levels are not elevated in asthmatic patients, compared with normal subjects (Chalmers *et al.,* 1997b). An increase in the concentration of plasma ET-1 has been reported in asthmatic children and adults and is related to asthma severity (Aoki *et al.,* 1994; Chen *et al.,* 1995), although another study showed no increase in plasma ET-1 levels in patients with mild asthma (Chalmers *et al.,* 1997b). Furthermore, in patients with nocturnal asthma, there is a significantly

lower level of ET-1 in bronchoalveolar lavage fluid at night than during the day (Kraft *et al.,* 1994). There is a significant increase in the expression of ET-1 immunoreactivity in the epithelial layer in fiber-optic bronchial biopsies from asthmatic patients (Springall *et al.,* 1991). It is tempting to speculate that this is the result of the action of proinflammatory cytokines (IL-1β, TNF-α, and IL-6) released from activated macrophages in asthmatic airways. Anti-CD23 also induces release of ET-1 in epithelial cells from asthmatic patients, suggesting that allergen acting via a low affinity IgE receptor (FcϵRII) may be a mechanism for releasing ET-1 in asthma (Campbell *et al.,* 1994). There is also an increase in the ET-1 content of alveolar macrophages from asthmatic patients, compared with normal subjects, although there is no increase in the release of ET-1 after stimulation with lipopolysaccharide (Chanez *et al.,* 1996).

b. EFFECTS OF INHIBITORS. Several nonpeptide antagonists have been developed for clinical use (Warner *et al.,* 1996), but they have not yet been tested in asthmatic patients. Because bronchoconstriction is mediated by ET_B receptors but the remodeling effects are mediated by ET_A receptors, it is likely that a nonselective antagonist would be preferable. Potent nonpeptide antagonists, such as SB217242, have been developed and may be more suitable as drugs. If the major effect of ETs is in tissue remodeling, it may be difficult to test the efficacy of such compounds, because very prolonged studies may be needed. In a guinea pig model of asthma, the early and late responses to inhaled allergen are reduced by ET receptor antagonists; the early bronchoconstriction response is blocked by ET_B receptor antagonists, whereas the late inflammatory response is reduced by ET_A receptor antagonists (Uchida *et al.,* 1996). In mice, an ET_A receptor antagonist but not an ET_B receptor antagonist reduces allergen-induced eosinophilic responses, apparently via an increase in IFN-γ release (Fujitani *et al.,* 1997). This suggests that it might be possible to assess ET receptor antagonists by measuring allergen-induced responses. Glucocorticoids inhibit the expression of ET-1 in epithelial cells of asthmatic patients (Vittori *et al.,* 1992) and in animal lungs (Andersson *et al.,* 1992), suggesting that treatment with inhaled corticosteroids may reduce ET synthesis in asthma. ET-1 levels in bronchoalveolar lavage fluid from asthmatic patients treated with inhaled corticosteroids are lower than those in fluid from patients not treated with steroids (Redington *et al.,* 1997a).

c. CONCLUSIONS. ET-1 is abnormally expressed in asthma and is likely to contribute to its pathophysiological mechanism. Although ET-1 is a potent bronchoconstrictor and induces plasma exudation and mucus secretion, its most striking effect is on airway remodeling. ET receptor antagonists have been developed for clinical application and may be useful in the treatment of asthma, although their benefits may be difficult to assess in clinical trials, because they may affect the long term progression of asthma.

E. Complement

1. Synthesis and metabolism. The complement system contains a series of 30 distinct circulating proteins, including proteolytic proenzymes, nonenzymatic components that form functional enzymes when activated, and receptors (Ember and Hugli, 1997). The proenzymes become sequentially activated in a cascade that finally leads to the formation of the so-called terminal attack sequence, which can promote cell lysis and is central to our defense against invading microorganisms. However, there are several by-products generated during the activation of the complement cascade that have proinflammatory activity and therefore have the potential to be involved in asthma. The larger fragments of C3 and C4 (i.e., C3b and C4b) are involved in a range of biological activities, including opsonization, phagocytosis, and immunomodulation. There are also several smaller fragments generated during the activation of C5, such as C3a and C5a, which have been referred to as anaphylatoxins and which have several airway effects (Ember and Hugli, 1997).

2. Receptors. There are distinct receptors for C3a and C5a, which have been cloned (Ember and Hugli, 1997). Both are members of the G protein-coupled receptor superfamily.

3. Effects on airways. C3a and C5a induce airway smooth muscle contraction and chemotaxis of leukocytes, including eosinophils (Daffern *et al.,* 1995; Regal, 1997). Aerosolization of C5a into the airways induces transient hyperresponsiveness to inhaled histamine (Irvin *et al.,* 1986; Armour *et al.,* 1987), an effect that is partially inhibited by pretreatment with indomethacin (Berend *et al.,* 1986). Both C3a and C5a are potent stimulants of eosinophil degranulation (Takafuji *et al.,* 1996), and the response of circulating eosinophils to C5a is enhanced after the late response to inhaled allergen in asthmatic patients (Evans *et al.,* 1996b). C5a is also a potent chemoattractant of human monocytes and may therefore be involved in recruitment of macrophages into asthmatic airways (Pieters *et al.,* 1995).

4. Role in asthma. There have been conflicting reports regarding changes in the complement cascade in asthmatic patients (Barnes *et al.,* 1988). An increased amount of C3a has been demonstrated in the circulation of asthmatics during exercise-induced bronchoconstriction (Smith *et al.,* 1990), and increased levels of C3a have been demonstrated in bronchoalveolar lavage fluid obtained from some, but not all, asthmatics (Van de Graaf *et al.,* 1992). Furthermore, patients with severe asthma have been reported to show increased serum levels of C3a and to exhibit a different pattern of complement activation, compared with patients with bronchial infections (Lin *et al.,* 1992). In asthmatic patients, the neutrophil chemotactic activity of bronchoalveolar

lavage fluid is largely explained by C5a (Teran *et al.,* 1997), suggesting that this is an important mediator of neutrophilic infiltration in asthmatic airways.

Evaluation of the contribution of endogenous activation of complement to the allergic asthmatic response is difficult, because there are no selective inhibitors for the various complement components. However, in experimental animals, treatment with soluble complement receptor 1, the normal regulator of circulating C1, reduces allergen-induced bronchoconstriction (Regal *et al.,* 1993). Treatment of animals with cobra venom factor to deplete circulating complement components does not inhibit allergen-induced eosinophilic infiltration into lungs, however (Regal and Fraser, 1996).

V. Small Molecules

A. Reactive Oxygen Species

There is increasing evidence that oxidative stress and reactive oxygen species (ROS) are involved in inflammatory airway diseases, including asthma (Barnes, 1990; Repine *et al.,* 1997), although relatively few studies have been undertaken in humans. This is partly because of the difficulties of measuring oxidative stress in the airways in vivo and partly because of the relative inefficacy of currently available antioxidants. However, new noninvasive techniques have been developed to assess oxidative stress in the airways, making it possible to reassess the role of oxidative stress in asthma.

1. Synthesis and metabolism. Many inflammatory and structural cells that are activated in asthmatic airways, including eosinophils, macrophages, mast cells, and epithelial cells, produce ROS (Barnes, 1990). Superoxide anions are generated by NADPH oxidase and then are converted to hydrogen peroxide by superoxide dismutases (SODs). Hydrogen peroxide is then degraded to water by catalases. Superoxide and hydrogen peroxide may interact in the presence of free iron to form the highly reactive hydroxyl radical. Superoxide may also combine with NO to form peroxynitrite, which also generates hydroxyl radicals (Beckman and Koppenol, 1996). Oxidative stress describes an imbalance between ROS and antioxidants. The normal production of oxidants is counteracted by several antioxidant mechanisms in the human respiratory tract (Cantin *et al.,* 1990). The major intracellular antioxidants in the airways are catalase, SOD, and glutathione, which is formed by the selenium-dependent enzyme glutathione peroxidase. Extracellular antioxidants include the dietary antioxidants vitamin C (ascorbic acid) and vitamin E (α-tocopherol), uric acid, and lactoferrin. Oxidant stress activates the inducible enzyme heme oxygenase-1, which converts heme and hemin to biliverdin, with the formation of carbon monoxide (Wong and Wispe, 1997; Choi and Alam, 1996). Biliverdin is converted, by bilirubin reductase, to bilirubin, which is a potent antioxidant.

2. Effects on airways.

a. AIRWAY SMOOTH MUSCLE. Hydrogen peroxide directly constricts airway smooth muscle in vitro, and this effect is mediated partly via the release of prostanoids (Rhoden and Barnes, 1989). ROS may damage airway epithelium, resulting in increased epithelial shedding and increased bronchoconstriction responses (Yukawa *et al.,* 1990). In vitro, hydrogen peroxide induces an increase in the responsiveness of human airways (Hulsmann *et al.,* 1994a). Formation of peroxynitrite also increases airway responsiveness in guinea pigs in vitro and in vivo (Sadeghi-Hashjin *et al.,* 1996), but its effect in human airways is not yet known.

b. VESSELS. Little is known regarding the effects of ROS on the bronchial vasculature. Hydroxyl radical potently induces plasma exudation in rodent airways (Lei *et al.,* 1996).

c. SECRETIONS. The effects of ROS on mucus secretion have not yet been investigated in human airways. In rats, oxidative stress increases airway mucus secretion, an effect that is blocked by COX inhibitors (Adler *et al.,* 1990).

d. NERVES. Allergen impairs the function of bronchodilating nerves in guinea pig airways in vivo by an effect that is blocked by SOD, suggesting that superoxide anions may scavenge NO released from motor nerves (Miura *et al.,* 1997). In rat airways, oxidant stress increases cholinergic nerve-induced bronchoconstriction, an effect that may be the result of oxidative damage to acetylcholinesterase (Ohrui *et al.,* 1991).

e. INFLAMMATORY CELLS. Oxidants also activate NF-κB (which orchestrates the expression of multiple inflammatory genes that undergo increased expression in asthma), thereby amplifying the inflammatory response (Barnes and Karin, 1997). Many of the stimuli that activate NF-κB appear to do so via the formation of ROS, particularly hydrogen peroxide (Schreck *et al.,* 1991). ROS activate NF-κB in an epithelial cell line (Adcock *et al.,* 1994) and increase the release of proinflammatory cytokines from cultured human airway epithelial cells (Rusznak *et al.,* 1996).

ROS and peroxynitrite induce lipid peroxidation, resulting in the formation of additional mediators. Isoprostanes are derived from lipid peroxidation of arachidonic acid (Morrow and Roberts, 1996). The most prevalent isoprostane is 8-epi-$PGF_{2\alpha}$, which is a potent constrictor of human airways in vitro, acting predominantly via Tx receptors, as discussed above (Kawikova *et al.,* 1996).

3. Role in asthma.

a. RELEASE. Bronchoalveolar lavage fluid cells from asthmatic patients show increased production of superoxide anions, compared with cells from normal individuals (Jarjour and Calhoun, 1994), and this production is increased further after allergen challenge (Calhoun and Bush, 1990). Increased generation of superoxide has also been reported for circulating monocytes and neutrophils

from asthmatic patients (Vachier *et al.,* 1994), and there is evidence for increased oxidative stress in the circulation (Rahman *et al.,* 1996). Circulating eosinophils from asthmatic patients produce excessive superoxide after activation (Chanez *et al.,* 1990), and this is increased even further after allergen challenge (Evans *et al.,* 1996b). In experimental animals, certain viral infections (e.g., influenza) induce various indices of oxidative stress in the lungs (Choi and Alam, 1996), and this may be relevant to exacerbations of asthma.

It has recently become possible to measure oxidative stress using less invasive or noninvasive procedures, facilitating more detailed exploration of these factors in asthma. Hydrogen peroxide levels in exhaled condensates are increased in asthmatic adults and children (Dohlman *et al.,* 1993; Jobsis *et al.,* 1997; Antczak *et al.,* 1997; Horvath *et al.,* 1998) and are increased further during exacerbations (Dohlman *et al.,* 1993). An increase in exhaled carbon monoxide levels has been reported for patients with asthma (Zayasu *et al.,* 1997). Other noninvasive markers include thiobarbituric acid-reactive substances, which are produced as a result of lipid peroxidation and are increased in exhaled condensates from asthmatic patients (Antczak *et al.,* 1997). Pentane, another product of lipid peroxidation, is also increased in the exhaled air from asthmatic patients during exacerbations of asthma (Olopade *et al.,* 1997). There is immunocytochemical evidence for peroxynitrite formation in asthmatic airways, obtained using an antibody to nitrotyrosine that detects nitrosylated proteins and demonstrates increased immunoreactivity in the airway mucosa, particularly in epithelial cells (Giaid *et al.,* 1998).

In addition to the increased production of ROS in asthma, there may be a deficiency in antioxidant defenses. Glutathione peroxidase activity is reduced in platelets from asthmatic patients and this reduction is correlated with a reduction in serum selenium concentrations (Powell *et al.,* 1994; Misso *et al.,* 1996), but there is a surprising increase in glutathione levels in bronchoalveolar lavage fluid from asthmatic patients (Smith *et al.,* 1993). SOD activity is reduced in bronchoalveolar lavage fluid cells and epithelial cells from asthmatic patients, without any change in catalase activity (Smith and Harrison, 1997). There is reduced SOD activity in airway epithelial cells from asthmatic patients, because of reduced expression of Cu/Zn-SOD, possibly from oxidative inactivation (de Raeve *et al.,* 1997). Interestingly, there are no abnormalities in antioxidant levels in asthmatic patients who achieve control with inhaled corticosteroids. There is increasing epidemiological evidence that a lack of dietary antioxidants may be an important determinant of asthma (Greene, 1995). Population surveys have shown that a low dietary intake of the antioxidant vitamin C is associated with poorer lung function and increased prevalence of wheezing (Britton *et al.,* 1995; Cook *et al.,* 1997). A low intake of vitamin C is associated with increased bronchial reactivity (Soutar *et al.,* 1997), consistent with the proposal that the increased prevalence of asthma may be a result of reductions in the dietary intake of antioxidants (Seaton *et al.,* 1995). Another study reported a weak association between low vitamin E intake and asthma (Troisi *et al.,* 1995).

b. EFFECTS OF INHIBITORS. Several antioxidants have also been administered to asthmatic patients, to explore the effects of these compounds on lung function and airway reactivity. There have been several short term studies with vitamin C showing small beneficial effects on either lung function or airway reactivity, but no measurements of inflammation have been made (Bielory and Gandhi, 1994). There have been no formal trials of vitamin E or of another antioxidant, N-acetylcysteine. Selenium administered for a 3-month period to patients with chronic asthma produced a small but significant improvement in clinical symptoms but no improvement in lung function or airway reactivity (Hasselmark *et al.,* 1993). Currently available antioxidants are rather weak, but more potent drugs, including spin-trap antioxidants (nitrones) and stable glutathione analogues, are currently in clinical development.

B. Nitric Oxide

There is increasing evidence that endogenous NO plays a key role in physiological regulation of airway functions and is implicated in airway diseases, including asthma (Barnes and Belvisi, 1993; Gaston *et al.,* 1994; Barnes, 1995b).

1. Synthesis and metabolism. NO is a gas that is derived from the amino acid L-arginine by the enzyme NOS, of which at least three isoforms exist (Nathan and Xie, 1994). There are two cNOS forms; one was first described in brain and is localized to neural tissue [neuronal NOS (nNOS) or NOSI], and the other is localized to endothelial cells [endothelial NOS (eNOS) or NOSIII], although it has become apparent that both enzymes are also expressed in other cells, such as epithelial cells. Both enzymes are activated by increases in $[Ca^{2+}]_i$ and produce small amounts of NO, which serve a local regulatory function. In contrast, iNOS (NOSII) is not normally expressed but is induced by inflammatory cytokines and endotoxin. This enzyme form is less dependent on increases in $[Ca^{2+}]_i$, because calmodulin is tightly bound to the enzyme; when the enzyme is induced it is activated and produces much larger amounts of NO than do cNOS isoforms. NO produced by cNOS is involved in physiological regulation of airway function, whereas NO produced by iNOS is involved in inflammatory diseases of the airways and in host defenses against infection.

Immunohistological studies have identified the presence of all three isoforms of NOS in human airways (Kobzik *et al.,* 1993; Ward *et al.,* 1995b; Giaid *et al.,* 1998). eNOS is localized to endothelial cells in the bronchial circulation, but there is also evidence for eNOS

expression in epithelial cells (Shaul *et al.,* 1994). nNOS is localized to cholinergic nerves in airways (Fischer *et al.,* 1993) but has also been reported in epithelial cells (Asano *et al.,* 1994). iNOS may be expressed in several types of cells in response to cytokines, endotoxin, or oxidants (Morris and Billiar, 1994). In asthmatic airways, there is increased immunocytochemical staining for iNO, which is localized predominantly to airway epithelial cells (Hamid *et al.,* 1993), and there is also localization to inflammatory cells, including macrophages and eosinophils (Giaid *et al.,* 1998).

NO may be produced by several types of cells in the airways. In primary cultured human airway epithelial cells, proinflammatory cytokines increase NO production and increase iNOS immunoreactivity and mRNA levels (Robbins *et al.,* 1994; Asano *et al.,* 1994; Guo *et al.,* 1995). In a human epithelial cell line (A549) and in rat type II pneumocytes, oxidants and ozone increase iNOS expression (Adcock *et al.,* 1994; Punjabi *et al.,* 1994). This is associated with activation of NF-κB, which is involved in the transcription of many inflammatory and immune genes (Barnes and Karin, 1997). NF-κB is of critical importance in increasing the transcription of the iNOS gene (Xie *et al.,* 1994) and may be activated in several types of pulmonary cells by proinflammatory cytokines. Glucocorticoids inhibit the induction of iNOS in epithelial cells, and this is likely to be via a direct inhibitory interaction between the activated glucocorticoid receptor and NF-κB (Barnes and Karin, 1997). Eosinophils also express iNOS and release nitrite (del Pozo *et al.,* 1997). It has proven difficult to induce iNOS in human, compared with rodent, macrophages. In human monocytes, anti-CD23 antibody causes release of nitrite, suggesting that allergens may trigger iNOS expression (Aubry *et al.,* 1997), and similar results are seen in alveolar macrophages from normal and asthmatic subjects (Donnelly *et al.,* 1998).

Progress in understanding the role of NO in health and disease has been largely dependent on the development of specific NOS inhibitors. The first inhibitors to be developed were analogues of L-arginine, such as L-NMMA and N^G-nitro-L-arginine methyl ester (L-NAME) (which are nonselective inhibitors of NOS), and aminoguanidine (which selectively inhibits iNOS). More potent and selective inhibitors are now in development.

NO is rapidly transformed to nitrite and nitrate, which may be used to monitor NO production. NO also rapidly combines with superoxide anions to form peroxynitrite, which is highly reactive, nitrosylates proteins, and forms hydroxyl radicals (Beckman and Koppenol, 1996). Nitrosylation of tyrosine residues on proteins and nitrotyrosine may be detected immunocytochemically, providing evidence of local generation of peroxynitrite (Beckman and Koppenol, 1996). The presence of nitrotyrosine has recently been demonstrated in asthmatic airways, providing evidence for peroxynitrite generation within the airways. The amount of nitrotyrosine immunostaining is correlated with airway hyperresponsiveness, as measured by methacholine challenge (Giaid *et al.,* 1998).

2. Receptors. NO does not have conventional receptors but, rather, diffuses into cells and activates soluble guanylyl cyclase, resulting in an increase in the formation of cyclic GMP. In airway smooth muscle, cyclic GMP causes relaxation (Ward *et al.,* 1995a). Some of the effects of NO are mediated by the formation of peroxynitrite, as discussed above.

3. Effects on airways. NO has many effects on airway function, although the effects of endogenous NO depend on the site of production and the amount produced (Barnes, 1996b).

a. AIRWAY SMOOTH MUSCLE. NO and NO donor compounds relax human airway smooth muscle in vitro via activation of guanylyl cyclase and increases in cyclic GMP levels (Ward *et al.,* 1995a; Gaston *et al.,* 1993). High concentrations of inhaled NO produce bronchodilation and protect against cholinergic bronchoconstriction in guinea pigs in vivo (Dupuy *et al.,* 1992). In humans, inhalation of high concentrations of NO (80 ppm) has no effect on lung function in normal subjects and produces only weak and variable bronchodilation in asthmatic patients (Högman *et al.,* 1993; Sanna *et al.,* 1994; Kacmarek *et al.,* 1996). NO may, however, be the major neurotransmitter of bronchodilating nerves in human airways. In proximal human airways, there is a prominent inhibitory NANC (i-NANC) bronchodilating neural mechanism, which assumes particular functional importance because it is the only endogenous bronchodilating pathway in human airways. The neurotransmitter of this i-NANC pathway in human airways is NO, because NOS inhibitors virtually abolish this neural response (Belvisi *et al.,* 1992a,b; Bai and Bramley, 1993). Furthermore, i-NANC stimulation of human airways results in an increase in cyclic GMP levels without any increase in cyclic AMP levels (Ward *et al.,* 1995a). The density of nNOS-immunoreactive nerves is greatest in proximal airways and diminishes peripherally, which is consistent with a reduction in i-NANC responses in more peripheral airways (Ward *et al.,* 1995b). NOS is predominantly localized to parasympathetic (cholinergic) nerves and may be colocalized with vasoactive intestinal polypeptide (VIP), although the functional role of endogenous VIP in human airways is obscure (Belvisi *et al.,* 1992b).

b. VESSELS. NO is a potent vasodilator in the bronchial circulation and may play an important role in regulating airway blood flow, as in the pulmonary circulation (Higenbottam, 1995; Crawley *et al.,* 1990; Liu *et al.,* 1991; Martinez *et al.,* 1995). Endogenous NO may increase the exudation of plasma by increasing blood flow to leaky postcapillary venules, thus increasing airway edema (Kuo *et al.,* 1992b). However, NOS inhibitors applied to the airway surface increase plasma exudation, suggesting that basal release of NO has an inhibitory effect on

microvascular leakage (Erjefält *et al.,* 1994). This paradox is resolved by considering the differing effects of NO, depending on the amount produced. In rat airways, L-NAME increases basal leakiness, whereas after endotoxin exposure, when iNOS is induced, L-NAME inhibits leakage (Bernareggi *et al.,* 1997). Thus, the effect of endogenous NO on plasma exudation may depend on the amount produced and the site of production. In the context of asthma, the increased production of NO is likely to result in increased plasma exudation. Furthermore, if peroxynitrite is generated in asthma, this may lead to the formation of hydroxyl radicals that also increase airway plasma exudation (Lei *et al.,* 1996).

c. SECRETIONS. L-NAME increases basal airway mucus secretions, suggesting that NO produced by cNOS normally inhibits mucus secretion (Ramnarine *et al.,* 1996). However, NO donors increase mucus secretion in human airways in vitro (Nagaki *et al.,* 1995). In cultured guinea pig airways after exposure to TNF-α and other inflammatory stimuli, there is increased secretion of mucus, which is inhibited by L-NMMA, suggesting that large amounts of NO generated by iNOS stimulate mucus secretion (Adler *et al.,* 1995). Endogenous NO may also be important in regulating mucociliary clearance, because a NOS inhibitor decreases ciliary beat frequency in bovine airway epithelial cells (Jain *et al.,* 1993).

d. NERVES. NO may be released with acetylcholine from cholinergic nerves and may modulate cholinergic neural responses. NOS inhibitors increase cholinergic neural bronchoconstriction in human and guinea pig airways (Belvisi *et al.,* 1991, 1993; Ward *et al.,* 1993). However, this appears to be the result of functional antagonism at the level of airway smooth muscle, rather than an effect on acetylcholine release from cholinergic nerves (Brave *et al.,* 1991; Ward *et al.,* 1993).

e. INFLAMMATORY CELLS. High concentrations of NO are cytotoxic and are involved in basic defenses against microorganisms. Targeted disruption ("knock-out") of the iNOS gene in mice results in a marked increase in susceptibility to infections (Wei *et al.,* 1995; Laubach *et al.,* 1995). It is possible that NO is toxic to epithelial cells in the airways and may contribute to epithelial shedding in asthma. These effects are likely to be mediated by the formation of peroxynitrite.

There is increasing evidence that high concentrations of NO may have effects on the immune system and the inflammatory response. NO inhibits Th1 lymphocytes in mice and thus favors the development of a Th2 response, with eosinophilia (Taylor-Robinson *et al.,* 1993; Barnes and Liew, 1995). There is also evidence that NO promotes the chemotaxis of eosinophils, because L-NAME blocks eosinophil recruitment in the lungs (Ferreira *et al.,* 1996). NO-donor compounds increase the survival of eosinophils by inhibiting apoptosis (Beauvais *et al.,* 1995), and NO inhibits Fas receptor-mediated apoptosis in these cells (Hebestreit *et al.,* 1998).

4. Role in asthma.

a. RELEASE. There is evidence for increased expression of iNOS in asthmatic airways, particularly in epithelial cells and macrophages (Hamid *et al.,* 1993; Giaid *et al.,* 1998). It is likely that this arises from the effects of proinflammatory cytokines, oxidants, and perhaps other inflammatory mediators. Because NO is a gas, it diffuses into the airway lumen and may be detected in exhaled air (Barnes and Kharitonov, 1996). There is an increase in NO levels in the exhaled air from asthmatic patients (Alving *et al.,* 1993; Kharitonov *et al.,* 1994; Persson *et al.,* 1994), which is derived from the lower airways (Kharitonov *et al.,* 1996b; Massaro *et al.,* 1996). The increased exhaled NO in asthma is related to airway inflammation (Jatakanon *et al.,* 1998), is increased during the late response to allergen (Kharitonov *et al.,* 1995) and during exacerbations (Massaro *et al.,* 1995), and is decreased by treatment with inhaled corticosteroids (Kharitonov *et al.,* 1996a).

b. EFFECTS OF INHIBITORS. Although exhaled NO is a useful noninvasive marker of inflammation in asthma, it is less certain how endogenous NO contributes to the pathophysiological mechanisms of asthma. Single inhalations of L-NMMA and L-NAME (via a nebulizer) result in reduced exhaled NO levels for normal and asthmatic patients (Kharitonov *et al.,* 1994; Yates *et al.,* 1995, 1996). Interestingly, there is no fall in forced expiratory volume in 1 sec, even in asthmatic patients with highly reactive airways, suggesting that basal production of NO is not important in maintaining basal airway tone. Although infusion of L-NMMA in normal subjects causes an increase in blood pressure, neither nebulized L-NAME nor L-NMMA has any effect on heart rate or blood pressure, suggesting that inhibition of NOS is confined to the respiratory tract. Although L-NMMA and L-NAME are nonselective inhibitors of cNOS and iNOS, aminoguanidine has some selectivity for iNOS. Inhalation of aminoguanidine has no effect on exhaled NO levels of normal subjects but significantly reduces exhaled NO levels of patients with asthma (Yates *et al.,* 1996), further supporting the view that the elevated levels of exhaled NO in asthma are produced by iNOS. More potent and selective iNOS inhibitors are now in clinical development (Garvey *et al.,* 1997).

c. CONCLUSIONS. There is good evidence for increased formation of NO in asthma, as evidenced by the high levels of NO in exhaled air, compared with normal subjects, and the fact that this increase is correlated with eosinophilic inflammation. NO is a potent vasodilator and may increase plasma exudation. It may also participate in the inflammatory response by shifting the balance toward Th2 cells and by recruiting and increasing the survival of eosinophils in the airways. Use of the potent selective iNOS inhibitors now in clinical development should reveal the importance of NO in asthma.

VI. Cytokines

A. General Overview

1. The cytokine network in chronic inflammation. Cytokines are small protein mediators that play an integral role in the coordination and persistence of inflammation in asthma, although the precise role of each cytokine remains to be determined. The chronic airway inflammation of asthma is unique, in that the airway wall is infiltrated by T lymphocytes of the Th2 phenotype, eosinophils, macrophages/monocytes, and mast cells. In addition, "acute-on-chronic" inflammation may be observed in acute exacerbations, with increases in eosinophils and neutrophils and release of mediators such as histamine and cys-LTs from eosinophils and mast cells, to induce bronchoconstriction, airway edema, and mucus secretion.

Th2 lymphocytes produce a panel of cytokines, including IL-3, IL-4, IL-5, IL-9, IL-10, IL-13, and GM-CSF. The primary signals that activate Th2 cells are unknown but may be related to the presentation of a restricted panel of antigens in the presence of appropriate cytokines. Dendritic cells are ideally suited to act as the primary contacts between the immune system and external allergens. Interaction of co-stimulatory molecules on the surface of antigen-presenting cells (in particular, the B7.2/CD28 interaction) may lead to proliferation of Th2 cells, thus perpetuating mast cell activation and eosinophilic inflammation. This may lead to the production of specific IgE by B lymphocytes under the influence of IL-4, which plays a critical role in the isotype switching of B lymphocytes from IgG to IgE production. Other cytokines, including TNF-α and IL-6, may also be important. The IgE produced in asthmatic airways binds to FcϵRI on mast cells, priming them for activation by antigen. The development of mast cells from bone marrow cells represents a process of maturation and expansion, involving growth factors and cytokines [such as stem cell factor (SCF) and IL-3] produced by structural cells. Mast cells recovered from asthmatic patients by bronchoalveolar lavage show increased release of mediators such as histamine.

IL-4 also increases the expression of an inducible form of the low affinity receptor for IgE (FcϵRII or CD23) on B lymphocytes and macrophages. This may account for the increased expression of CD23 on alveolar macrophages from asthmatic patients, which in turn could account for the increased release of cytokines from these macrophages. In addition, IL-4 is very important in driving the differentiation of $CD4^+$ Th precursors into Th2-like cells.

The differentiation, migration, and pathobiological effects of eosinophils may occur through the effects of GM-CSF, IL-3, and IL-5. Once recruited from the circulation, mature eosinophils in the presence of these cytokines change phenotype into hypodense eosinophils, which show increased survival in bronchial tissue. These eosinophils are primed for ligand-initiated generation of increased amounts of cys-LTs and for cytotoxicity to other cells, such as those of the airway epithelium. Eosinophils themselves may also generate other cytokines.

Cytokines may also play an important role in antigen presentation and may enhance or suppress the ability of macrophages to act as antigen-presenting cells. Airway macrophages are normally poor at antigen presentation and suppress T cell proliferative responses [possibly via release of cytokines such as IL-1 receptor antagonist (IL-1ra)], but in asthma there is evidence for reduced suppression after exposure to allergen (Spiteri *et al.,* 1994; Aubus *et al.,* 1984). Both GM-CSF and IFN-γ increase the ability of macrophages to present allergen and express HLA-DR (Fischer *et al.,* 1988). IL-1 is important in activating T lymphocytes and is an important co-stimulator of the expansion of Th2 cells after antigen presentation (Chang *et al.,* 1990). Airway macrophages may be an important source of "first wave" cytokines, such as IL-1, TNF-α, and IL-6, which may be released (via FcϵRII) upon exposure to inhaled allergens. These cytokines may then act on epithelial cells to release a second wave of cytokines, including GM-CSF, IL-8, and the regulated on activation, normal T cell-expressed, and secreted protein (RANTES), which amplify the inflammatory response and lead to influx of secondary cells such as eosinophils, which themselves may release multiple cytokines.

Cytokines may also exert an important regulatory effect on the expression of adhesion molecules, both on endothelial cells of the bronchial circulation and on airway epithelial cells. IL-4 increases the expression of vascular cell adhesion molecule-1 (VCAM-1) on endothelial and airway epithelial cells, and this may be important in eosinophil and lymphocyte trafficking (Schleimer *et al.,* 1992). IL-1 and TNF-α increase the expression of ICAM-1 in both vascular endothelium and airway epithelium (Tosi *et al.,* 1992).

Another feature of the chronic inflammation of asthma is the proliferation of myofibroblasts and the hyperplasia of airway smooth muscle. The mechanisms by which these structural changes occur are unclear, but several growth factors, such as platelet-derived growth factor (PDGF) and TGF-β, may be released from inflammatory cells in the airways (such as macrophages and eosinophils) and also from structural cells (such as airway epithelial cells, endothelial cells, and fibroblasts). These growth factors may stimulate fibrogenesis by recruiting and activating fibroblasts or transforming myofibroblasts. There is particular interest in the possibility that epithelial cells may release growth factors, because collagen deposition occurs underneath the basement membrane of the airway epithelium (Brewster *et al.,* 1990). Growth factors may also stimulate the proliferation and growth of airway smooth muscle cells. PDGF and EGF are potent stimulants of animal and human

airway smooth muscle proliferation (Hirst *et al.,* 1992; Knox, 1994), and these effects are mediated by activation of tyrosine kinase and PKC. Growth factors may also be important in the proliferation of mucosal blood vessels and the goblet cell hyperplasia that are characteristic of chronically inflamed asthmatic airways. Cytokines such as TNF-α and fibroblast growth factors (FGFs) may also play important roles in the angiogenesis that is observed in chronic asthma.

Therefore, many cytokines are involved in the development of the atopic state and the chronic inflammatory processes of asthma, ultimately contributing to the release of mediators such as histamine and cys-LTs, airway remodeling, bronchoconstriction, and bronchial hyperresponsiveness (table 2). The role of each cytokine in these processes can be evaluated by studying its properties, its presence and localization in the airway wall and in airway secretions of patients with asthma, and the effects of specific inhibitors, such as receptor antagonists or specific antibodies. Although these cytokines work in concert, the important cytokines implicated in asthma are considered separately. It is difficult to categorize these cytokines because they often have pleiotropic and overlapping effects. With respect to asthma and allergy, the following groupings are used in this review: (*a*) lymphokines, i.e., IL-2, IL-3, IL-4, IL-5, IL-13, IL-15, IL-16, and IL-17; (*b*) proinflammatory cytokines, i.e., IL-1, TNF, IL-6, IL-11, GM-CSF, and SCF; (*c*) anti-inflammatory cytokines, i.e., IL-10, IL-1ra, IFN-γ, IL-12, and 1L-18; and (*d*) growth factors, i.e., PDGF, TGF-β, FGF, EGF, and insulin-like growth factor (IGF). Chemotactic cytokine (chemokines) are discussed in Section VII.

This section deals with the cytokines that appear to be most involved in asthma. Their synthesis and release, receptors, effects with particular relevance to asthma, and potential role in asthma are discussed. As for the classical mediators, the potential role of each cytokine can be judged from its expression in asthmatic airways, from studies with transgenic or knock-out mice, or from

TABLE 2
Effects of cytokines in asthma

Cytokine	Eosinophil activation	T lymphocyte activation	Other cell activation	IgE control	AHR[a]
Lymphokines					
IL-2	Eosinophilia in vivo	Growth and differentiation of T cells	Monocytes/macrophages, B cells, lymphokine-activated killer cells		++
IL-3	Eosinophilia in vivo		Pluripotential hematopoietic factor		?
IL-4	↑ eosinophil growth	↑ Th2, ↓ Th1	B cells, monocytes/macrophages, endothelium	↑ IgE	+
IL-5	Eosinophil maturation, ↓ apoptosis	↑ Th2 cells	Eosinophils		++
IL-13	Activates eosinophils, ↓ apoptosis		Monocytes, B cells	↑ IgE	?
IL-15	As for IL-2	Growth and differentiation of T cells	Activation of neutrophils and monocytes	?	?
IL-16	Eosinophil migration	Growth factor and chemotaxis of T cells ($CD4^+$)	?		?
IL-17		T cell proliferation	Activation of epithelial and endothelial cells, fibroblasts	?	?
Proinflammatory cytokines					
IL-1	↑ adhesion to vascular endothelium, eosinophil accumulation in vivo	Growth factor for Th2 cells	B cell growth factor, neutrophil chemoattractant, T cell and epithelial cell activation		+
TNF-α			Epithelium, endothelium, antigen-presenting cells, monocytes/macrophages		+
IL-6		T cell growth factor	B cell growth factor	↑ IgE	?
IL-11		?	B cell growth factor, activation of fibroblasts		+
GM-CSF	Eosinophil apoptosis and activation, induces release of LTs		Proliferation and maturation of hematopoietic cells, endothelial cell migration		+
SCF	↑ VCAM-1 on eosinophils		Growth factor for mast cells		–
Inhibitory cytokines					
IL-10	↓ eosinophil survival	↓ Th1 and Th2	↓ monocyte/macrophage activation, ↑ B cells, ↑ mast cell growth		↓
IL-1ra		↓ Th2 proliferation			↓
IFN-γ	↓ eosinophil influx after allergen	↓ Th2 cells	Endothelial cells, epithelial cells, alveolar macrophages/monocytes	↓ IgE	↓
IL-12	↓ eosinophil influx after allergen	↑ activated T cells, ↑ Th1, ↓ Th2	↑ natural killer cells	↓ IgE	↓
IL-18	↓ via IFN-γ release	Releases IFN-γ from Th1 cells	Activation of natural killer cells and monocytes	↓ IgE	?↓
Growth factors					
PDGF			Fibroblast and ASM proliferation, release of collagen		?
TGF-β		↓ T cell proliferation, blocks IL-2 effects	Fibroblast proliferation, chemoattractant for monocytes, fibroblasts, and mast cells, ↓ ASM proliferation		?

[a] AHR, airway hyperresponsiveness; +, modest effect; ++, marked effect; ASM, airway smooth muscle.

studies involving the use of synthesis inhibitors, antibodies, or blockers at the receptor level.

2. Cytokine receptors. The receptors for many cytokines have now been cloned and, based on common homology regions, these have been grouped into superfamilies (Kishimoto *et al.,* 1994).

a. CYTOKINE RECEPTOR SUPERFAMILY. This largest receptor superfamily includes IL-2 receptor β- and γ-chains, IL-4 receptor, IL-3 receptor α- and β-chains, IL-5 α- and β-chains, IL-6 receptor, gp130, IL-12 receptor, and GM-CSF receptor. The extracellular regions of the cytokine receptor family contain combinations of cytokine receptor domains, fibronectin type III domains, and usually C2 Ig constant region-like domains. Some members are composed of a single polypeptide chain that binds its ligand with high affinity. For other receptors, there may be more than one binding site for the ligand (typically sites with high and low binding affinities). For these receptors, additional subunits that are required for high affinity receptor expression have been identified. Some of these subunits are shared by more than one cytokine receptor, giving rise to heterodimeric structures. Such examples include (*a*) receptors sharing the GM-CSF receptor β-chain (IL-3, IL-5, and GM-CSF); (*b*) receptors sharing the IL-6 receptor β-chain, gp130 (IL-6, leukemia inhibitory factor, and oncostatin M); and (*c*) receptors sharing the IL-2 receptor γ-chain (IL-2, IL-4, IL-7, and IL-15).

Many proteins of the cytokine receptor superfamily are secreted as soluble forms, which are produced by alternative splicing of their mRNA transcripts to yield proteins lacking the transmembrane region and the cytoplasmic proximal charged residues that anchor the protein into the membrane. They may act as antagonists, as transport proteins to carry cytokines to other sites, or as agonists.

b. IMMUNOGLOBULIN SUPERFAMILY. Cytokine receptors with Ig superfamily domains in their extracellular sequences include IL-1, IL-6, PDGF, and GM-CSF receptors. The Ig domains are characterized by a structural unit of approximately 100 amino acids, with a distinct folding pattern known as the Ig fold.

c. PROTEIN KINASE RECEPTOR SUPERFAMILY. These receptors have glycosylated, extracellular, ligand-binding domains, a single transmembrane domain, and an intracellular, tyrosine kinase catalytic domain. The superfamily includes receptors for growth factors such as PDGF, EGF, and FGF.

d. INTERFERON RECEPTOR SUPERFAMILY. This group includes the IFN-α/β receptor, IFN-γ receptor, and IL-10 receptor. They are single-transmembrane domain glycoproteins that are characterized by either one (IFN-γ and IL-10 receptors) or two (IFN-α/β receptors) homologous extracellular regions. Signal transduction involves phosphorylation and activation of Janus protein kinase and tyrosine kinase 2 protein tyrosine kinases.

e. NERVE GROWTH FACTOR RECEPTOR SUPERFAMILY. These cytokine receptors include the nerve growth factor receptor, TNF receptor-I (p55), and TNF receptor-II (p75). These are characterized by three or four cysteine-rich repeats of approximately 40 amino acids in the extracellular part of the molecule. The mode of signal transduction has not been elucidated.

f. SEVEN-TRANSMEMBRANE DOMAIN G PROTEIN-COUPLED RECEPTOR SUPERFAMILY. These receptors include the chemokine receptors, which have a characteristic structure of a relatively short, acidic, extracellular, amino-terminal sequence followed by seven transmembrane domains with three extracellular and three intracellular loops. The receptors are coupled to heterotrimeric G proteins, which induce PI phosphate hydrolysis and activate kinases, phosphatases, and ion channels.

B. Lymphokines

Lymphokines are cytokines that are produced by T lymphocytes, although it is now recognized that many other cell types may release these cytokines. They play an important role in immunoregulation.

1. Interleukin-2.

a. SYNTHESIS AND RELEASE. Activated T cells, particularly Th0 and Th1 T cells, are major sources of IL-2 (Morgan *et al.,* 1976), whereas B lymphocytes can be induced under certain conditions to secrete IL-2 in vitro. IL-2 is secreted by antigen-activated T cells 4 to 12 h after activation, accompanied later by up-regulation of high affinity IL-2 receptors on the same cells. Binding of IL-2 to IL-2 receptors induces proliferation of T cells, secretion of cytokines, and enhanced expression of receptors for other growth factors, such as insulin. The IL-2-receptor complex is then removed from the T cell surface by internalization. IL-2 can also be produced by eosinophils (Levi Schaffer *et al.,* 1996) and by airway epithelial cells (Aoki *et al.,* 1997).

b. RECEPTORS. The IL-2 receptor complex is composed of three chains (α, β, and γ) and belongs to the family of hematopoietic cytokine receptors (Taniguchi and Minami, 1993; Weiss and Littman, 1994). The α- and β-chains bind to IL-2 with low affinity, whereas the γ-chain does not bind IL-2 alone. The high affinity complex is an $\alpha\beta\gamma$ heterotrimer, whereas $\alpha\gamma$ and $\beta\gamma$ heterodimers have intermediate affinities. The β-chain, which is expressed constitutively in T lymphocytes, is essential for signal transduction, and the intracellular domain has critical sequences necessary for growth-promoting signals (Hatakeyama *et al.,* 1989). The γ-chain also appears to be important for signal transduction (Zurawski and Zurawski, 1992), whereas the α-chain alone is unable to transduce any signal.

c. EFFECTS. IL-2 stimulates the growth and differentiation of T cells, B cells, natural killer cells, lymphokine-activated cells, and monocytes/macrophages. IL-2 functions as an autocrine growth factor for T cells and also exerts paracrine effects on other T cells (Smith,

1988). IL-2 is also involved in T cell receptor-stimulated T cell apoptosis (Lenardo, 1991). IL-2 promotes the differentiation and Ig secretion of B cells. IL-2 acts on monocytes to increase IL-1 secretion, cytotoxicity, and phagocytosis (Smith, 1988). Experiments with IL-2 gene knock-out mice show that these animals develop a normal thymus and normal T cell subpopulations in peripheral tissues, indicating that IL-2 activity is redundant and not confined to IL-2 alone (Schorle *et al.,* 1991). Together with IL-4, IL-2 can reduce the glucocorticoid receptor binding affinity of blood mononuclear cells (Sher *et al.,* 1994). IL-2 stimulates natural killer cells to secrete IFN-γ, to proliferate, and to increase cytolysis. IL-2 enhances GM-CSF production in peripheral blood mononuclear cells from asthmatics and IL-5 production in T cells from patients with the hypereosinophilic syndrome (Nakamura *et al.,* 1993; Enokihara *et al.,* 1989). IL-2 is a potent chemoattractant for eosinophils in vitro (Rand *et al.,* 1991b).

Systemic infusion of IL-2 as part of chemotherapeutic treatment results in eosinophilia, with an associated increase in eosinophil colony-stimulating activity (Sedgwick *et al.,* 1990; Macdonald *et al.,* 1990). This activity was abolished by neutralizing antibodies to IL-3, IL-5, or GM-CSF, indicating that IL-2 acts indirectly by promoting the synthesis of these substances. Repeated administration of IL-2 induces bronchial hyperresponsiveness in Lewis rats (Renzi *et al.,* 1991). In ovalbumin-sensitized Brown-Norway rats, IL-2 led to a 3-fold increase in the late-phase response, compared with the response in rats receiving only saline before allergen exposure (Renzi *et al.,* 1992). IL-2 caused an inflammatory response around the airways, with a significant increase in eosinophils, lymphocytes, and mast cells.

d. ROLE IN ASTHMA. Levels of IL-2 are increased in bronchoalveolar lavage fluid from patients with symptomatic asthma (Walker *et al.,* 1992; Broide *et al.,* 1992b). Increased bronchoalveolar lavage cells expressing IL-2 mRNA are also present (Robinson *et al.,* 1992), and a nonsignificant increase in IL-2 mRNA-positive cells is observed in asthmatics after allergen challenge (Bentley *et al.,* 1993). Particularly high levels of IL-2 and IL-4 mRNA-positive bronchoalveolar lavage cells are observed in steroid-resistant asthmatics, compared with steroid-sensitive asthmatics (Leung *et al.,* 1995); this increase is not abolished by pretreatment with oral prednisolone for the steroid-resistant patients, and there are no differences in the expression of IL-5 and IFN-γ mRNA between the two groups.

Cyclosporin A, which inhibits IL-2 gene transcription in activated T lymphocytes through interference with the transcription factors AP-1 and NF-AT, inhibits allergic airway eosinophilia but not bronchial hyperresponsiveness in animal models (Elwood *et al.,* 1992). However, for patients with severe asthma, cyclosporin A causes a reduction in the amount of oral steroid therapy needed to control asthmatic symptoms (Alexander *et al.,* 1992), although this finding was not confirmed in another study (Nizankowska *et al.,* 1995). These effects of cyclosporin A may result from inhibition of IL-2 expression, as well as inhibition of the expression of other cytokines, such as GM-CSF and IL-5.

2. Interleukin-3.

a. SYNTHESIS AND RELEASE. Activated Th cells are the predominant source of IL-3, together with mast cells (Arai *et al.,* 1990; Fung *et al.,* 1984).

b. RECEPTORS. The IL-3 receptor is formed by the association of a low affinity IL-3-binding α-subunit with a β-subunit, which is common to the IL-5 and GM-CSF receptors but does not itself bind to these cytokines (Hayashida *et al.,* 1990). IL-3 binding to its receptor results in rapid tyrosine and serine/threonine phosphorylation of several cellular proteins, including the IL-3 receptor β-subunit itself (Isfort *et al.,* 1988; Sorensen *et al.,* 1989). A monoclonal antibody to the IL-3 receptor α-chain abolishes its function (Sun *et al.,* 1996). The human IL-3 receptor is expressed on myeloid, lymphoid, and vascular endothelial cells. It is selectively induced in human endothelial cells by TNF-α, and it potentiates IL-8 secretion and neutrophil transmigration (Korpelainen *et al.,* 1993).

c. EFFECTS. IL-3 is a pluripotent hematopoietic growth factor that, together with other cytokines such as GM-CSF, stimulates the formation of erythroid cell, megakaryocyte, neutrophil, eosinophil, basophil, mast cell, and monocytic lineages (Ottmann *et al.,* 1989). GM-CSF also increases the responsiveness of neutrophils to IL-3 (Smith *et al.,* 1995). Mice that overexpress IL-3 show only modest eosinophilia but die early because of massive tissue infiltration and destruction by myeloid cells such as neutrophils and macrophages (Dent *et al.,* 1990).

d. ROLE IN ASTHMA. An increase in the number of cells expressing IL-3 mRNA has been reported in mucosal biopsies and in bronchoalveolar lavage cells from patients with asthma (Robinson *et al.,* 1992,1993a). However, after inhalation challenge, the number of IL-3 mRNA-positive cells does not increase, in contrast to those expressing IL-5 (Bentley *et al.,* 1993).

3. Interleukin-4.

a. SYNTHESIS AND RELEASE. IL-4 is produced by Th2-derived T lymphocytes and certain populations of thymocytes, as well as eosinophils and cells of the basophil and mast cell lineages. Cross-linking of the CD40 ligand on human $CD4^+$ T cells from normal nonallergic subjects generates a co-stimulatory signal that increases IL-4 synthesis (Blotta *et al.,* 1996). Synthesis can also be induced by stimulation of the antigen receptor on T lymphocytes and by IgE Fc receptor cross-linking in mast cells and basophils. Interestingly, corticosteroids enhance the capacity to induce IL-4 synthesis from $CD4^+$ T cells (Blotta *et al.,* 1997).

b. RECEPTORS. The IL-4 receptor is a complex consisting of two chains, a high affinity IL-4-binding chain

(p140, α-chain), which binds IL-4 and transduces its growth-promoting and transcription-activating functions (Galizzi *et al.,* 1990; Idzerda *et al.,* 1990), and the IL-2 receptor γ-chain (the common γ-chain, γc), which amplifies signaling of the IL-4 receptor (Russell *et al.,* 1993; Kondo *et al.,* 1993). The α-chain belongs to the cytokine receptor superfamily. A recombinant extracellular domain of the human IL-4 receptor is a potent IL-4 antagonist (Garrone *et al.,* 1991). The IL-2 receptor γ-chain augments IL-4 binding affinity (Kondo *et al.,* 1993; Russell *et al.,* 1993). A low affinity IL-4 receptor has also been identified (Fanslow *et al.,* 1993). High affinity IL-4 receptors are abundant in activated B and T cells. They are also present on hematopoietic progenitor cells, mast cells, macrophages, endothelial cells, epithelial cells, fibroblasts, and muscle cells (Park *et al.,* 1987a,b; Ohara and Paul, 1987).

IL-4 induces phosphorylation of the IL-4-induced phosphotyrosine substrate, which is associated with the p85 subunit of phosphatidylinositol-3 kinase and with Stat-6 and Janus protein kinase after cytokine stimulation (Imani *et al.,* 1997; Hatakeyama *et al.,* 1991; Wang *et al.,* 1992, 1993). The transcription factor Stat-6 is essential for mediation of the effects of IL-4 (Takeda *et al.,* 1996; Shimoda *et al.,* 1996). IL-4 also stimulates PI hydrolysis, yielding IP_3 and subsequent calcium flux, followed by increased intracellular cyclic AMP levels (Finney *et al.,* 1990). Interestingly, an association with atopy has been found with a R567 allele of the IL-4 receptor α-subunit (Khuruna Hershey *et al.,* 1997), which enhances signaling and decreases the binding of the phosphotyrosine phosphatase Src homology 2-containing protein tyrosine phosphate (which has been implicated in termination of signaling by means of cytokine receptors) (Imani *et al.,* 1997; Paulson *et al.,* 1996).

c. EFFECTS. IL-4 plays an important role in B lymphocyte activation by increasing expression of class II major histocompatibility complex (MHC) molecules, as well as enhancing expression of CD23 (low affinity FcεRII), CD40, and the α-chain of the IL-2 receptor. It promotes Ig synthesis by B lymphocytes and plays a central role in Ig class switching of activated B lymphocytes to the synthesis of IgG4 and IgE. This switching is accompanied by germline ε-chain synthesis. IL-4 promotes the development of Th2-like $CD4^+$ T cells and inhibits the development of Th1-like T cells (Le Gros *et al.,* 1990; Swain *et al.,* 1990). It also enhances the cytolytic activity of $CD8^+$ cytotoxic T cells. Virus-specific $CD8^+$ T cells can be induced by IL-4 to produce IL-5 (Coyle *et al.,* 1995a).

IL-4 also exerts effects on monocytes and macrophages. It enhances the surface expression of MHC class II molecules and the antigen-presenting capacity of macrophages but inhibits the macrophage colony formation and release of TNF, IL-1, IL-12, IFN-γ, IL-8, and macrophage inflammatory protein (MIP)-1α. Together with other cytokines such as GM-CSF and IL-6, IL-4 can promote the growth of mast cell and myeloid and erythroid progenitors. IL-4 also up-regulates endothelial VCAM-1 expression on the endothelium. Interaction of VCAM-1 with very late activation antigen-4 promotes eosinophil recruitment (Schleimer *et al.,* 1992). IL-4 also induces fibroblast chemotaxis and activation (Postlethwaite *et al.,* 1992; Postlethwaite and Seyer, 1991) and, in concert with IL-3, IL-4 promotes the growth of human basophils and eosinophils (Favre *et al.,* 1990). IL-4 has inhibitory effects such as suppression of metalloproteinase biosynthesis in human alveolar macrophages (Lacraz *et al.,* 1992), inhibition of the expression of iNOS in human epithelial cells (Berkman *et al.,* 1996b), and reduction of RANTES and IL-8 expression in human airway smooth muscle cells (John *et al.,* 1997, 1998a).

d. ROLE IN ASTHMA. IL-4 has been shown to be expressed by $CD4^+$ and $CD8^+$ T cells, eosinophils, and mast cells in both atopic and nonatopic asthma (Bradding *et al.,* 1992; Ying *et al.,* 1997). Increased numbers of lymphocytes expressing IL-4 mRNA together with IL-5 mRNA in bronchoalveolar lavage fluid have been reported after allergen challenge (Robinson *et al.,* 1993a). No increased levels of IL-4 have been detected in bronchoalveolar lavage fluid of asthmatics (Broide *et al.,* 1992b). The potential importance of IL-4 in inducing allergic airway inflammation has been addressed with IL-4-knock-out mice. Sensitization and exposure to ovalbumin did not induce lung eosinophilia as it did in the wild-type littermates (Brusselle *et al.,* 1994). No ovalbumin-specific IgE was observed with active sensitization, and repeated exposures to ovalbumin did not induce bronchial hyperresponsiveness (Brusselle *et al.,* 1995). The crucial effects of IL-4 appear to lie in its effect on Th2 cell development. The development of airway inflammation in the murine model of allergen-induced airway inflammation is accompanied by the presence of Th2 cells in the airways (Coyle *et al.,* 1995b). In IL-4-knock-out mice, T cells recovered from the airways do not synthesize a Th2 cytokine pattern, which correlates with the absence of inflammatory airway changes. When wild-type mice are treated with anti-IL-4 during the exposure to aerosolized ovalbumin but not during the sensitization process, the influx of eosinophils to the airways is not inhibited (Corry *et al.,* 1996; Coyle *et al.,* 1995b). IL-4 receptor blockade prevents the development of antigen-induced airway hyperreactivity, goblet cell metaplasia, and pulmonary eosinophilia in a mouse model (Gavett *et al.,* 1997). Thus, IL-4 appears to be important in the early stages of Th2 cell development.

4. Interleukin-5.

a. SYNTHESIS AND RELEASE. IL-5 was first isolated from supernatants of activated murine spleen cells, which were shown to induce eosinophil colony formation. The isolated soluble activity was shown to selectively stimulate eosinophil production from murine bone marrow and was termed eosinophil differentiation factor. IL-5 was isolated from this soluble activity (Lopez *et al.,* 1986). IL-5 is produced by T lymphocytes; in asthmatic

airways, increased expression of IL-5 mRNA has been demonstrated in $CD4^+$ T cells, using in situ hybridization (Hamid *et al.,* 1991). Bronchoalveolar lavage $CD4^+$ and $CD8^+$ T cells can also secrete IL-5 (Till *et al.,* 1995). IL-5 mRNA has been detected in the sputum and bronchial biopsies from patients with asthma, but not nonasthmatic controls, using reverse transcription-polymerase chain reaction (Gelder *et al.,* 1993, 1995). In addition, human eosinophils can express IL-5 mRNA and release IL-5 protein in vitro (Dubucquoi *et al.,* 1994), and endobronchial challenge results in IL-5 mRNA expression in eosinophils in bronchoalveolar lavage fluid (Broide *et al.,* 1992b), with an increase in IL-5 concentrations of up to 300-fold (Ohnishi *et al.,* 1993b; Sedgwick *et al.,* 1991). Elevated IL-5 concentrations have been reported in bronchoalveolar lavage fluid from symptomatic but not asymptomatic asthmatics (Ohnishi *et al.,* 1993a). Increased circulating levels of immunoreactive IL-5 have been measured in the serum of patients with exacerbations of asthma, and these levels fall with corticosteroid treatment (Corrigan *et al.,* 1993). IL-5 levels are raised in induced sputum after allergen challenge of asthmatic patients (Keatings *et al.,* 1997). IL-5 protein has also been localized (by immunochemical analysis) in mast cells in bronchial biopsies of patients with asthma, together with IL-4, IL-6, and TNF-α (Bradding *et al.,* 1994). Transcriptional control of the human IL-5 gene involves several transcription factors, including NF-AT (Stranick *et al.,* 1997).

b. RECEPTORS. The human IL-5 receptor has been identified in vitro on eosinophils, basophils, and B lymphocytes but not on neutrophils or monocytes (Lopez *et al.,* 1991). It consists of a heterodimer with two polypeptide chains, i.e., a low affinity binding α-chain and a nonbinding β-chain shared with the IL-3 and GM-CSF receptors (Tavernier *et al.,* 1991). Both chains belong to the cytokine receptor superfamily (Bazan, 1990). The α-subunit alone is sufficient for ligand binding and is specific for IL-5, but association with the β-chain leads to a 2- to 3-fold increase in binding affinity and allows signaling to occur. Some IL-5 receptor mutants have antagonistic effects and may act as receptor antagonists (Tavernier *et al.,* 1995). Transcriptional regulation of the specific chain yields either membrane-bound or soluble forms of the receptor (Tavernier *et al.,* 1992). The membranous form interacts with the β-subunit, leading to substantial increases in affinity for IL-5 (Koike and Takatsu, 1994). The soluble form is secreted in body fluids, interacts with IL-5, and antagonizes the action of IL-5 on target cells (Devos *et al.,* 1993; Tavernier *et al.,* 1992). The expression of the IL-5 receptor is restricted to eosinophils and their immediate precursors. An increase in the number of both forms of IL-5 receptors in bronchial biopsies from asthmatics has been reported, with the expression of IL-5 receptor mRNA being predominantly in eosinophils (Yasruel *et al.,* 1997). Ligand binding to IL-5 receptors activates non-receptor protein tyrosine kinase and other protein kinases in eosinophils (Bates *et al.,* 1996; Taniguchi, 1995).

c. EFFECTS. IL-5 can influence the production, maturation, and activation of eosinophils (Egan *et al.,* 1996). IL-5 acts predominantly at the later stages of eosinophil maturation and activation (Clutterbuck *et al.,* 1989; Lopez *et al.,* 1988). IL-5 can also prolong the survival of eosinophils (Yamaguchi *et al.,* 1988). IL-5 appears to be the main cytokine involved in the development of eosinophilia in vivo. Administration of exogenous IL-5 produces eosinophilia in many in vivo models (Iwama *et al.,* 1992). IL-5-transgenic mice, in which transcription of IL-5 is coupled to the dominant control region of the gene coding for the constitutive marker CD2, show lifelong eosinophilia in organs with predicted T cell expression, such as bone marrow, spleen, and peritoneum, with fewer cells in the airway mucosa (Dent *et al.,* 1990). IL-5-knock-out transgenic mice behave normally, indicating that eosinophils require other factors for degranulation and subsequent tissue damage. Intratracheal administration of another eosinophil chemotactic agent, eotaxin, leads to further eosinophil accumulation in the lungs and bronchial hyperresponsiveness, an effect not observed in wild-type mice (Rothenberg *et al.,* 1996). IL-5 may cause eosinophils to be released from the bone marrow, whereas local release of another chemoattractant may be necessary to cause tissue localization of eosinophils (Collins *et al.,* 1995). On the other hand, IL-5 instilled into the airways of patients with asthma induces significant airway eosinophilia (Shi *et al.,* 1997), and inhaled IL-5 causes eosinophilia in induced sputum and bronchial hyperresponsiveness but has no effect on airway caliber (Shi *et al.,* 1998). The eosinophil chemotactic responses of bronchoalveolar lavage fluid of asthmatics during the pollen season is accounted for by IL-5 and RANTES (Venge *et al.,* 1996).

d. ROLE IN ASTHMA. IL-5 may play an important role in eosinophil maturation, chemoattraction, and activation in asthma and may underlie bronchial hyperreactivity. It may also interact with other eosinophil chemoattractants and activators, such as chemokines, to activate and induce chemoattraction of eosinophils (Rothenberg *et al.,* 1997; Collins *et al.,* 1995). The expression of IL-5 in tissues and cells from patients with asthma is discussed above. Studies with IL-5 monoclonal antibodies clearly support a role for IL-5 in asthma. Pretreatment with anti-IL-5 monoclonal antibodies can suppress allergen-induced airway eosinophilia (Chand *et al.,* 1992; Van Oosterhout *et al.,* 1993; Mauser *et al.,* 1993, 1995). There is some debate regarding whether the IL-5-induced eosinophilia is the direct cause of bronchial hyperresponsiveness induced by allergen exposure. There is an effect of anti-IL-5 antibodies on bronchial hyperresponsiveness in some studies (Van Oosterhout *et al.,* 1993; Mauser *et al.,* 1995), whereas other studies do not report such an effect, despite inhibition of eosinophilia (Corry *et al.,* 1996). In IL-5-knock-out mice, both

allergen-induced eosinophilia and airway hyperresponsiveness are abolished (Foster *et al.,* 1996). The site of IL-5 expression may be critical to eosinophil recruitment and the development of airway hyperresponsiveness. Studies of transgenic mice expressing IL-5 from lung epithelial cells showed elevated levels of IL-5 in bronchoalveolar lavage fluid and serum, lung histopathological changes reminiscent of asthma, and base-line airway hyperresponsiveness (Lee *et al.,* 1997). In addition to the effect of IL-5 in mobilizing eosinophils from the bone marrow, there is evidence for its effect as a regulator of eosinophil homing and migration into tissues in response to local chemokine release (Mould *et al.,* 1997).

Studies of the use of anti-IL-5 antibodies in the treatment of human asthma are currently underway. Studies of the effect of systemic corticosteroid treatment in patients with worsening asthma indicate that there is a reduction in the expression of IL-5 mRNA in the airway mucosa that is associated with an improvement in asthma (Robinson *et al.,* 1993b). Cyclosporin A and tacrolimus (FK-506) (immunosuppressant agents sometimes used in the treatment of severe asthma) inhibit the expression of IL-5 mRNA in activated human T lymphocytes in response to phytohemagglutinin or phorbol esters (Rolfe *et al.,* 1997).

5. Interleukin-13.

a. SYNTHESIS AND RELEASE. IL-13 is synthesized by activated $CD4^+$ and $CD8^+$ T cells and is a product of Th1, Th2, and Th0-like $CD4^+$ T cell clones (Minty *et al.,* 1993a). Both $CD4^+$ and $CD8^+$ T cell clones synthesize IL-13 in response to antigen-specific or polyclonal stimuli (Zurawski and de Vries, 1994).

b. RECEPTORS. There is a close similarity between IL-4 and IL-13 receptors. An IL-4 receptor antagonist derived from a mutant protein (Zurawski *et al.,* 1993) is a potent receptor antagonist of the biological activity of IL-4 and also of IL-13. It particularly inhibits the effect of IL-13 in inducing IgE synthesis in peripheral blood mononuclear cells. There is evidence from cDNA cloning of the IL-13 receptor to suggest that the IL-4 receptor α-chain is a component of the IL-13 receptor (Aman *et al.,* 1996). Despite this, these receptors appear to be distinct (Zurawski and de Vries, 1994).

c. EFFECTS. IL-13 is a potent modulator of human monocyte and B cell function (Minty *et al.,* 1993a). IL-13 has profound effects on human monocyte morphological features, surface antigen expression, antibody-dependent cellular toxicity, and cytokine synthesis (McKenzie *et al.,* 1993; Minty *et al.,* 1993a). In human monocytes stimulated by lipopolysaccharide, the production of proinflammatory cytokines, chemokines, and colony-stimulating factors is inhibited by IL-13, whereas IL-1ra secretion is increased (Zurawski *et al.,* 1993). Production of IL-1β, IL-6, IL-8, IL-10, IL-12, IFN-γ, and GM-CSF from blood monocytes is inhibited (Berkman *et al.,* 1996c; de Waal Malefyt *et al.,* 1993), whereas MIP-1α, IL-1, and TNF-α release from human alveolar macrophages is inhibited (Yanagawa *et al.,* 1995; Berkman *et al.,* 1995). IL-13 inhibits the release of RANTES and IL-8 from airway smooth muscle cells in vitro (John *et al.,* 1997, 1998a). These actions of IL-13 are similar to those of IL-4 and IL-10. The suppressive effects of IL-13 and of IL-4 are not related to endogenous production of IL-10. Similarly to IL-4, IL-13 decreases the transcription of IFN-γ and IL-12. It is possible that IL-13 acts like IL-4 and suppresses the development of Th1 cells by down-regulating IL-12 production by monocytes, thereby favoring the development of Th2 cells (Le Gros *et al.,* 1990; Swain *et al.,* 1990; Hsieh *et al.,* 1994). IL-13, unlike IL-4, fails to activate human T cells, which appears to be the result of a lack of IL-13 receptors on these cells. IL-13 diminishes monocyte glucocorticoid receptor binding affinity (Spahn *et al.,* 1996). IL-13 activates eosinophils by inducing the expression of CD69 cell surface protein and prolonging eosinophil survival (Luttmann *et al.,* 1996).

IL-13 induces the expression of CD23 on purified human B cells and acts as a switch factor directing IgE synthesis, similar to IL-4 (Punnonen *et al.,* 1993; Cocks *et al.,* 1993). A mutant protein of IL-4, which is a potent receptor antagonist of the biological activity of IL-4, antagonizes IL-13 actions, blocking B cell proliferation and IgE synthesis (Aversa *et al.,* 1993). This mutant protein of IL-4 may therefore have therapeutic potential for the treatment of allergies.

d. ROLE IN ASTHMA. Increased expression of IL-13 mRNA has been reported in the airway mucosa of patients with atopic and nonatopic asthma (Humbert *et al.,* 1997a; Naseer *et al.,* 1997). In addition, levels of IL-13 together with IL-4 are increased after segmental allergen challenge of patients with asthma (Kroegel *et al.,* 1996). There is a significant correlation between eosinophil counts and levels of IL-13.

6. Interleukin-15.

a. SYNTHESIS AND RELEASE. IL-15 is produced by both $CD4^+$ and $CD8^+$ T cells after activation (Grabstein *et al.,* 1994). IL-15 mRNA is expressed in lung fibroblasts and epithelial cell lines, as well as monocytes and human blood-derived dendritic cells (Jonuleit *et al.,* 1997).

b. RECEPTORS. IL-15 uses the β- and γ-subunits of the IL-2 receptor (Giri *et al.,* 1994; Grabstein *et al.,* 1994), and both chains are needed for IL-15-mediated actions. A high affinity IL-15 binding subunit has also been described (Kennedy and Park, 1996). Mitogen-activated macrophages, natural killer cells, and $CD4^+$ and $CD8^+$ T cells express IL-15 receptor α-chains, which can bind IL-15 without requiring IL-2 receptor α- or β-chains (Chae *et al.,* 1996).

c. EFFECTS. IL-15 shares some of the properties of IL-2, such as stimulation of the proliferation of T cells and lymphokine-activated killer cells. However, there are many other distinct effects of IL-15. IL-15 can induce IL-8 and macrophage chemotactic peptide (MCP)-1 production in human monocytes (Badolato *et al.,* 1997). It

also induces the release of soluble IL-2 receptor α-chain from human blood mononuclear cells (Treiber Held *et al.,* 1996). It promotes angiogenesis in vivo (Angiolillo *et al.,* 1997). IL-15 can also activate neutrophils and delay their apoptosis (Girard *et al.,* 1996). IL-15 promotes the synthesis of IL-5 from house dust mite-specific human T cell clones (Mori *et al.,* 1996), an effect inhibited by the tyrosine kinase inhibitor herbimycin A. This indicates that IL-15 produced at the site of allergic inflammation may play a role in recruitment and activation of eosinophils by inducing IL-5 production by T cells. IL-15 is also a chemoattractant for human blood T lymphocytes, an effect inhibited by an anti-IL-2 receptor β-chain antibody (Wilkinson and Liew, 1995).

d. ROLE IN ASTHMA. There are no data specific to asthma.

7. Interleukin-16.

a. SYNTHESIS AND RELEASE. IL-16, previously known as lymphocyte chemoattractant factor, was first identified as a product of peripheral blood mononuclear cells after mitogen and histamine stimulation in vitro (Center *et al.,* 1983; Center and Cruikshank, 1982). IL-16 was subsequently shown to be produced by $CD8^+$ T cells after stimulation with histamine and serotonin in vitro (Laberge *et al.,* 1995, 1996). IL-16 can also be produced by epithelial cells (Bellini *et al.,* 1993), eosinophils (Lim *et al.,* 1996), and mast cells (Rumsaeng *et al.,* 1997).

b. EFFECTS. IL-16 has specific activities on $CD4^+$ T cells (Cruikshank *et al.,* 1994). IL-16 selectively induces migration of CD4+ cells, including $CD4^+$ T cells and CD4-bearing eosinophils (Rand *et al.,* 1991a). IL-16 acts as a growth factor for $CD4^+$ T cells and induces IL-2 receptors and MHC class II molecules on these cells (Cruikshank *et al.,* 1987).

c. ROLE IN ASTHMA. Elevated concentrations of IL-16 have been found in bronchoalveolar lavage fluid obtained from asthmatic subjects after allergen challenge (Cruikshank *et al.,* 1995b). In stable atopic asthmatic subjects, there is predominant expression of IL-16 mRNA and immunoreactivity in airway epithelium (Laberge *et al.,* 1997). IL-16-like activity has been detected in cell culture supernatants generated from histamine-stimulated tracheal epithelial cells obtained from asthmatic subjects (Bellini *et al.,* 1993).

8. Interleukin-17. IL-17 is a $CD4^+$ T cell-derived cytokine that stimulates NF-κB and IL-6 production in fibroblasts and co-stimulates T cell proliferation (Yao *et al.,* 1995a). It stimulates epithelial, endothelial, and fibroblastic cells to secrete cytokines such as IL-6, IL-8, GM-CSF, and PGE_2 (Fossiez *et al.,* 1996; Yao *et al.,* 1995b). In the presence of IL-17, fibroblasts can sustain the proliferation of $CD34^+$ hematopoietic progenitors and their preferential maturation into neutrophils. IL-17 increases the release of NO in cartilage from patients with osteoarthritis, via NF-κB activation (Attur *et al.,* 1997).

C. Proinflammatory Cytokines

Proinflammatory cytokines are involved in most types of inflammation and appear to amplify and perpetuate the ongoing inflammatory response. They may be important in disease severity and resistance to anti-inflammatory therapy in asthma.

1. Interleukin-1.

a. SYNTHESIS AND RELEASE. There are two distinct forms of IL-1 (α and β), produced from two different genes. Although the amino acid sequence homology between human IL-1α and IL-1β is only 20%, the molecules bind to the same receptor and have nearly identical properties. IL-1β (17.5 kDa) is synthesized as a larger precursor molecule with a molecular mass of 31 kDa. IL-1β is released into the extracellular space and the circulation. The most active form of IL-1β is its cleaved mature form, resulting from the action of a cysteine protease (IL-1-converting enzyme) (Thornberry *et al.,* 1992; Cerretti *et al.,* 1992). In contrast, IL-1α is usually retained intracellularly.

IL-1 is produced by a variety of cells, including monocytes/macrophages, fibroblasts, B cells, both Th1 and Th2-like T cell lines, natural killer cells, neutrophils, endothelial cells, and vascular smooth muscle cells. The major source of IL-1 in most tissues is stimulated monocytes/macrophages. Monocytes produce 10 times more IL-1β than IL-1α (Nishida *et al.,* 1987; March *et al.,* 1985); IL-1α is mostly cell-associated, whereas IL-1β is mostly released. Eosinophils can produce IL-1α (Weller *et al.,* 1993), whereas human epithelial cells can augment IL-1β expression when exposed to the air pollutant nitrogen dioxide (Devalia *et al.,* 1993). A wide variety of stimuli, including IL-1 itself (Dinarello and Mier, 1987), TNF-α (Turner *et al.,* 1989), GM-CSF (Xu *et al.,* 1989), endotoxin, and phagocytosis, can increase the expression of IL-1 in monocytes/macrophages. IL-1 production by endothelial and vascular smooth muscle cells can also be induced by IL-1β, TNF-α, or endotoxin. On the other hand, PGE_2 and corticosteroids can attenuate the capacity of endotoxin and other stimuli to release IL-1, through inhibition of transcription and through a decrease in IL-1 mRNA stability (Knudsen *et al.,* 1986; Pennington *et al.,* 1992; Kern *et al.,* 1988). An inhibitor of IL-1-converting enzyme that inhibits the inflammatory responses to IL-1β has been described (Ray *et al.,* 1992).

b. RECEPTORS. Two IL-1 receptors have been described. The type I and type II receptors are transmembrane glycoproteins that bind IL-1α, IL-1β, and IL-1ra. The type I IL-1 receptor is expressed on many cells, including T cells, B cells, monocytes, natural killer cells, basophils, neutrophils, eosinophils, dendritic cells, fibroblasts, endothelial cells, and vascular endothelial cells, whereas the type II receptor is also expressed on T cells, B cells, and monocytes. An IL-1 receptor accessory protein has been described (Greenfeder *et al.,* 1995), which,

when associated with the type I IL-1 receptor, increases its affinity for IL-1β. Only the type I receptor transduces a signal in response to IL-1 (McKean *et al.,* 1993); the type II IL-1 receptor, on binding to IL-1, does not. Therefore, the type II IL-1 receptor may act as a decoy receptor, preventing IL-1 from binding to the type I IL-1 receptor (Colotta *et al.,* 1994). IL-1 signal transduction pathways are associated with TNF receptor-associated factor (TRAF) adaptor proteins, particularly TRAF-6 (Cao *et al.,* 1996a). TRAF-6 associates with IL-1 receptor-associated kinase, which is recruited to and activated by the IL-1 receptor complex (Cao *et al.,* 1996b).

A soluble receptor (found in normal human serum and secreted by the human B cell line RAJI) that binds preferentially to IL-1β has been described (Symons *et al.,* 1995). IL-1 down-regulates the numbers of IL-1 receptors (Matsushima *et al.,* 1986; Mizel *et al.,* 1981), whereas PGE_2 increases the expression of IL-1 receptors (Spriggs *et al.,* 1990; Bonin *et al.,* 1990). PDGF can increase IL-1 receptor expression and IL-1 receptor mRNA levels in fibroblasts (Chiou *et al.,* 1989; Bonin and Singh, 1988), whereas IL-4 increases receptor expression on T cells (Lacey and Erdmann, 1990). TGF-β may decrease the expression of IL-1 receptors (Dubois *et al.,* 1990) and may also uncouple the response of the cells to IL-1, without affecting IL-1 receptor expression or IL-1 binding (Stoeck *et al.,* 1990).

Some of the effects of IL-1 can be mimicked by agents that increase cyclic AMP levels and activate protein kinase A (Shirakawa *et al.,* 1986; Onozaki *et al.,* 1985), whereas others can be mimicked by agents that activate PKC (Emery *et al.,* 1989; Suzuki and Cooper, 1985; Shackelford and Trowbridge, 1984). Many cells produce cyclic AMP in response to IL-1. Activation of protein kinase A by an IL-1-induced increase in cyclic AMP levels may lead to increased transcription of several cellular genes. These may turn on activating transcription factors that bind to a *cis*-acting cyclic AMP-responsive element (Yamamoto *et al.,* 1988) and NF-κB, through the phosphorylation of an inhibitor protein, IκB. AP-1 activity may also be induced by IL-1 (Muegge *et al.,* 1989) through PKC activation. Phosphorylation of several cellular proteins through the action of PKC-independent serine/threonine kinase may also occur upon activation of the IL-1 receptor (Kaur and Saklatvala, 1988).

c. EFFECTS. IL-1 induces fever, like other endogenous pyrogens such as TNF and IL-6. It causes leukocytosis by release of neutrophils from the bone marrow and induces the production of other cytokines, including IL-6.

IL-1 is a growth factor for mature and immature thymocytes and a cofactor in the induction of proliferation of and IL-2 secretion by peripheral blood $CD4^+$ and $CD8^+$ T cells after engagement of their antigen receptors. IL-1β is an important growth factor for Th2 cells in response to antigen-primed antigen-presenting cells, but not for Th1 cells (Greenbaum *et al.,* 1988). Synergistic effects between IL-1 and IL-6 have been reported for the activation of T cells (Helle *et al.,* 1989; Elias *et al.,* 1989; Sironi *et al.,* 1989). IL-1 also functions as a growth factor for B cells (Paul and Ohara, 1987; Vink *et al.,* 1988; Lipsky *et al.,* 1983). IL-1 induces many other cytokines, such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, RANTES, GM-CSF, IFN-γ, PDGF, and TNF, in a variety of cells. IL-1 induces fibroblasts to proliferate (Schmidt *et al.,* 1982), an effect that may be the result of release of PDGF (Raines *et al.,* 1989), it increases PG synthesis and collagenase secretion (Postlethwaite *et al.,* 1983; Mizel *et al.,* 1981), and it increases the synthesis of fibronectin and types I, III, and IV collagen (Dinarello and Savage, 1989). IL-1β together with TNF-α and IFN-γ can induce or up-regulate the expression of ICAM-1 and VCAM-1 on endothelial cells and on respiratory epithelial cells, which may lead to increased adhesion of eosinophils to the vascular endothelium and respiratory epithelium (Godding *et al.,* 1995; Pober *et al.,* 1986). IL-1-induced adhesion of eosinophils to endothelial cell monolayers is inhibited by anti-ICAM and anti-VCAM antibodies (Bochner *et al.,* 1991).

d. ROLE IN ASTHMA. Levels of IL-1β in bronchoalveolar lavage fluid from patients with asthma have been found to be elevated, compared with those in fluid from nonasthmatic volunteers; there is also an increase in IL-1β-specific mRNA transcripts in bronchoalveolar lavage fluid macrophages (Borish *et al.,* 1992). In addition, patients with symptomatic asthma show increased levels of IL-1β in bronchoalveolar lavage fluid, compared with patients with asymptomatic asthma (Broide *et al.,* 1992b). Increased expression of IL-1β in asthmatic airway epithelium has been reported, together with an increased number of macrophages expressing IL-1β (Sousa *et al.,* 1996). Selective inhibition of IL-1β expression in the epithelium of the airway wall of patients with asthma, without a reduction in IL-1ra expression, after corticosteroid therapy has been described (Sousa *et al.,* 1997).

IL-1β induces airway neutrophilia and selectively increases airway responsiveness to bradykinin in rats (Tsukagoshi *et al.,* 1994a); these effects are mediated in part through the generation of ROS (Tsukagoshi *et al.*, 1994b). IL-1β can induce eosinophil accumulation in rat skin, an effect that is blocked by an anti-IL-8 antibody (Sanz *et al.,* 1995). Of interest, IL-1β has profound effects on the coupling of the β_2-adrenergic receptor to adenylyl cyclase, an effect that is mediated through the up-regulation of inhibitory G proteins (Koto *et al.,* 1996).

2. Tumor necrosis factor-α.

a. SYNTHESIS AND RELEASE. Two major forms of TNF exist, i.e., TNF-α and TNF-β, which have only 35% amino acid homology but bind to similar receptors. TNF-α (previously known as cachectin) is expressed as a type II membrane protein attached by a signal anchor transmembrane domain in the propeptide (Gearing *et*

al., 1994). TNF-α is released from cells by proteolytic cleavage of the membrane-bound form by a metalloproteinase (TNF-converting enzyme). Inactivation of the TNF-converting enzyme gene compromises the ability of cells to produce soluble TNF-α. TNF-α is produced by many cells, including macrophages, T lymphocytes, mast cells, and epithelial cells, but the principal source is macrophages. The secretion of TNF-α by monocytes/macrophages is greatly enhanced by other cytokines, such as IL-1, GM-CSF, and IFN-γ. Human eosinophils are also capable of releasing TNF-α (Costa *et al.,* 1993), together with airway epithelial cells (Devalia *et al.,* 1993). TNF-β is mainly produced by activated lymphocytes via a similar pathway.

b. RECEPTORS. TNF-α interacts with two cell surface receptors, i.e., p55 and p75. Both receptors are members of the nerve growth factor receptor superfamily. Soluble forms of human p55 and p75 receptors have been described; they are derived from the extracellular domains of the receptors and may act as inhibitors of TNF effects (Nophar *et al.,* 1990). TNF receptors are distributed on nearly all cell types except red blood cells and resting T lymphocytes. The p75 receptor is more restricted to hematopoietic cells. p75 is the principal receptor released by human alveolar macrophages and monocytes in the presence of IFN-γ (Galve de Rochemonteix *et al.,* 1996).

Several signaling pathways leading to activation of different transcription factors, such as NF-κB and AP-1, have been identified. The TRAF family of adaptor proteins, particularly TRAF-2, is involved in signaling from the TNF receptors (Rothe *et al.,* 1995). TRAF-2 may also play a role in the pathway of signal transduction from the TNF receptors to activation of the MAP kinase cascade. TNF activates a sphingomyelinase, resulting in the release of ceramide from sphingomyelin, which in turn activates a Mg^{2+}-dependent protein kinase (Mathias *et al.,* 1991).

c. EFFECTS. Many of the actions of TNF-α occur in combination with other cytokines as part of the cytokine network, and the effects of TNF-α are very similar to those of IL-1β, because there are close interactions between the signal transduction pathways of these two cytokines (Eder, 1997). TNF-α potently stimulates airway epithelial cells to produce cytokines, including RANTES, IL-8, and GM-CSF (Berkman *et al.,* 1995c; Kwon *et al.,* 1994a, 1995; Cromwell *et al.,* 1992), and it increases the expression of ICAM-1 (Tosi *et al.,* 1992). TNF-α also has synergistic effects with IL-4 and IFN-γ to increase VCAM-1 expression on endothelial cells (Thornhill *et al.,* 1991). This has the effect of increasing the adhesion of inflammatory leukocytes, such as neutrophils and eosinophils, at the airway surface. TNF-α enhances the expression of class II MHC molecules on antigen-presenting cells. In addition, it enhances the release of IL-1 by these cells. It acts as a co-stimulatory factor for activated T lymphocytes, enhancing proliferation and expression of IL-2 receptors. TNF-α also inhibits bone resorption and synthesis and induces proliferation of fibroblasts (Rogalsky *et al.,* 1992). TNF-α stimulates bronchial epithelial cells to produce tenascin, an extracellular matrix glycoprotein (Harkonen *et al.,* 1995).

d. ROLE IN ASTHMA. TNF-α may have an important amplifying effect in asthmatic inflammation (Kips *et al.,* 1993; Shah *et al.,* 1995). There is evidence for increased TNF-α expression in asthmatic airways (Bradding *et al.,* 1994), and IgE triggering in sensitized lungs leads to increased expression in epithelial cells in both rat and human lung (Ohkawara *et al.,* 1992; Ohno *et al.,* 1990). Increased TNF-α mRNA expression in bronchial biopsies from asthmatic patients has been reported (Ying *et al.,* 1991; Bradding *et al.,* 1994). TNF-α is also present in the bronchoalveolar lavage fluid from asthmatic patients (Broide *et al.,* 1992b), and TNF-α release from bronchoalveolar leukocytes from asthmatic patients is increased (Cembrzynska-Norvak *et al.,* 1993). TNF-α is also released from alveolar macrophages from asthmatic patients after allergen challenge (Gosset *et al.,* 1991). Furthermore, both blood monocytes and alveolar macrophages show increased gene expression of TNF-α after IgE triggering in vitro, and this effect is enhanced by IFN-γ (Gosset *et al.,* 1992). Alveolar macrophages of asthmatics undergoing late-phase responses after allergen challenge release more TNF-α and IL-6 ex vivo than do those from patients with only an early response (Gosset *et al.,* 1991). There are polymorphisms in the promoter of the TNF gene that may be more frequently associated with asthma (Moffatt and Cookson, 1997).

Infusion of TNF-α causes increased airway responsiveness in Brown-Norway rats (Kips *et al.,* 1992), and inhalation of TNF-α by normal human subjects results in increased airway responsiveness at 24 h after inhalation, as well as an increase in sputum neutrophils (Thomas *et al.,* 1995). TNF-α may be an important mediator in the initiation of chronic inflammation, by activating the secretion of cytokines from a variety of cells in the airways. Several approaches to inhibition of TNF-α synthesis or effects, including the use of monoclonal antibodies to TNF or soluble TNF receptors, in asthma are now under investigation.

3. Interleukin-6.

a. SYNTHESIS AND RELEASE. IL-6 was originally described for its antiviral activity, its effects on hepatocytes, and its growth-promoting effects on B lymphocytes and plasmacytomas. It is secreted by monocytes/macrophages, T cells, B cells, fibroblasts, bone marrow stromal cells, keratinocytes, and endothelial cells. Epithelial cells also appear to produce IL-6 (Mattoli *et al.,* 1991). Human airway smooth muscle cells, upon activation with IL-1β or TGF-β, can release IL-6 (Elias *et al.,* 1997). Major basic protein secreted from eosinophils can interact with IL-1 or TGF to increase IL-6 release from fibroblasts (Rochester *et al.,* 1996).

b. RECEPTORS. High affinity IL-6 receptors are formed by the association of the IL-6 receptor α-chain (which binds IL-6 with low affinity) with a β-chain (gp130) (which does not bind IL-6 but associates with the α-chain/IL-6 complex and is responsible for signal transduction) (Kishimoto *et al.,* 1992).

c. EFFECTS. IL-6 is a pleiotropic cytokine whose role in asthma remains unclear. IL-6 has growth-regulatory effects on many cells and is involved in T cell activation, growth, and differentiation. It is a terminal differentiation factor for B cells and induces Ig (IgG, IgA, and IgM) secretion (Akira *et al.,* 1993). IL-6 is an important cofactor in IL-4-dependent IgE synthesis (Vercelli *et al.,* 1989). IL-6 may also have anti-inflammatory effects. IL-6 can inhibit the expression and release of IL-1 and TNF from macrophages in vitro and can inhibit endotoxin-induced TNF production and neutrophil influx in the airways in vivo (Ulich *et al.,* 1991a,b; Schindler *et al.,* 1990a). IL-6-transgenic mice demonstrate lymphocytic infiltration around airways, which is associated with reduced airway responsiveness (DiCosmo *et al.,* 1994).

d. ROLE IN ASTHMA. IL-6 is released in asthma. There is evidence for increased release of IL-6 from alveolar macrophages from asthmatic patients after allergen challenge (Gosset *et al.,* 1991) and increased basal release, compared with nonasthmatic subjects (Broide *et al.,* 1992b). IgE-dependent triggering stimulates the secretion of IL-6 from both blood monocytes and alveolar macrophages in vitro (Gosset *et al.,* 1992). Increased levels of IL-6 can be measured in nasal washings from children after rhinovirus infection (Zhu *et al.,* 1996). In addition, IL-6 mRNA expression and an increase in NFκB DNA-binding activity can be induced by rhinovirus infection of cells in vitro.

4. Interleukin-11.

a. SYNTHESIS AND RELEASE. IL-11, which is distantly related to IL-6, is produced by fibroblasts and human airway smooth muscle cells when they are stimulated by IL-1 and TGF-β_1 (Maier *et al.,* 1993; Elias *et al.,* 1997).

b. RECEPTORS. A single class of specific receptors on mouse cells has been described (Yin *et al.,* 1992). The receptor has not yet been cloned. Like IL-6, IL-11 uses the IL-6 signal transducer gp130. Upon ligand binding, phosphorylation of tyrosine residues in several proteins occurs (Yin and Yang, 1993; Yin *et al.,* 1994).

c. EFFECTS. Although IL-11 cDNA was cloned on the basis of IL-6-like bioactivity, IL-11 has biological features distinct from those of IL-6. IL-11 promotes multiple stages of human megakaryocytopoeisis and thrombopoeisis. In combination with SCF or IL-4, IL-11 supports the generation of B cells (similarly to IL-6) (Hirayama *et al.,* 1992). IL-11 induces the production of acute-phase reactants (Baumann and Schendel, 1991). IL-11 induces the synthesis of the tissue inhibitor of metalloproteinase-1. It inhibits IL-12 and TNF-α production from monocytes/macrophages (Leng and Elias, 1997), effects mediated at the transcriptional level by inhibition of NF-κB.

d. ROLE IN ASTHMA. IL-11 is released into bronchoalveolar lavage fluid during upper respiratory viral infections in humans and induces nonspecific bronchial hyperresponsiveness in mice (Einarsson *et al.,* 1996). Targeted expression of IL-11 in mouse airways leads to a T cell inflammatory response with airway remodeling, local accumulation of myofibroblasts, and airway obstruction (Tang *et al.,* 1996).

5. Granulocyte-macrophage colony-stimulating factor.

a. SYNTHESIS AND RELEASE. GM-CSF is one of the colony-stimulating factors that act to regulate the growth, differentiation, and activation of hematopoietic cells of multiple lineages. GM-CSF is produced by several airway cells, including macrophages, eosinophils, T lymphocytes, fibroblasts, endothelial cells, airway smooth muscle cells, and epithelial cells.

b. RECEPTORS. The GM-CSF receptor consists of a low affinity α-chain and a β-chain that is shared with the IL-3 and IL-5 receptor α-chains (Kitamura *et al.,* 1991; Hayashida *et al.,* 1990). These receptors are usually distributed on granulocytes, monocytes, endothelial cells, and fibroblasts. Up-regulation of the expression of GM-CSF receptor α-chain mRNA in macrophages in airway biopsies from patients with nonatopic asthma, but not those with atopic asthma, has been reported (Kotsimbos *et al.,* 1997). Certain analogues of GM-CSF bind to the α-chain of the receptor, but not to the β-chain complex, without agonist effects, indicating that these mutants could act as antagonists of GM-CSF (Hercus *et al.,* 1994).

c. EFFECTS. GM-CSF is a pleiotropic cytokine that can stimulate the proliferation, maturation, and function of hematopoietic cells. GM-CSF may be involved in priming inflammatory cells, such as neutrophils and eosinophils. It can prolong the survival of eosinophils in culture (Hallsworth *et al.,* 1992). GM-CSF can enhance the release of superoxide anions and cys-LTs from eosinophils (Silberstein *et al.,* 1986). GM-CSF can also induce the synthesis and release of several cytokines, including IL-1 and TNF-α, from monocytes. GM-CSF induces nonhematopoietic cells, such as endothelial cells, to migrate and proliferate (Bussolino *et al.,* 1989).

d. ROLE IN ASTHMA. There is evidence for increased expression of GM-CSF in the epithelium in bronchial biopsies from asthmatic patients (Sousa *et al.,* 1993) and in T lymphocytes and eosinophils after endobronchial challenge with allergen (Broide and Firestein, 1991; Broide *et al.,* 1992a). Increased circulating concentrations of GM-CSF have been detected in patients with acute severe asthma (Brown *et al.,* 1991), and peripheral blood monocytes from asthmatic patients secrete increased amounts of GM-CSF (Nakamura *et al.,* 1993). In addition to its release in asthmatic airways, GM-CSF can be demonstrated to have various effects in asthma. GM-CSF has been found to be the major LTC_4-enhanc-

ing activity for eosinophils in the supernatant of cultured asthmatic alveolar macrophages (Howell *et al.,* 1989). Media obtained from cultured bronchial epithelial cells from asthmatics increase the viability, superoxide production, and LTC_4 production of eosinophils in vitro (Soloperto *et al.,* 1991), an effect that is abolished by a neutralizing antibody to GM-CSF. Transient expression of the GM-CSF gene in the epithelium of rats, using an adenoviral vector, leads to an accumulation of eosinophils and macrophages that is associated with irreversible fibrosis (Xing *et al.,* 1996). This indicates that GM-CSF may be involved in the chronic eosinophilia and airway remodeling of asthma.

6. Stem cell factor.

a. SYNTHESIS AND RELEASE. SCF (previously known as c-Kit ligand) is produced by bone marrow stromal cells, fibroblasts (including bronchial subepithelial myofibroblasts and nasal polyp fibroblasts), and epithelial cells, such as nasal polyp epithelial cells (Kim *et al.,* 1997; Zhang *et al.,* 1996; Galli *et al.,* 1994).

b. RECEPTORS. The receptor for SCF is c-Kit, a receptor protein kinase. It is expressed on early hematopoietic progenitor cells and allows a synergistic response to SCF and lineage-committing growth factors (such as GM-CSF for myelocytes). Expression of c-Kit decreases with cell maturation and is absent from mature cells released from the bone marrow. However, c-Kit expression increases on mast cells as they mature, and receptors are abundantly expressed on the surface of mast cells. c-Kit is also expressed on human eosinophils (Yuan *et al.,* 1997).

c. EFFECTS. SCF acts as a survival factor for the early hematopoietic progenitor cells and synergizes with other growth factors to regulate the proliferation and differentiation of cells. SCF is a major growth factor for human mast cells (Valent *et al.,* 1992; Mitsui *et al.,* 1993). Two alternative splice variants account for the different forms of SCF; one is primarily membrane bound and the other is primarily soluble, after being released from the cell surface by proteolysis (Flanagan *et al.,* 1991). $CD34^+$ bone marrow cells cultured in vitro with recombinant human SCF and IL-3 induce the development of mast cells and other hematopoietic lineages (Kirshenbaum *et al.,* 1992).

Membrane-bound SCF may influence mast cell adhesion (Kinashi and Springer, 1994), and soluble SCF is chemotactic for mast cells (Nilsson *et al.,* 1994). Removal of either soluble or membrane-bound SCF from mast cells causes the mast cells to undergo apoptosis (Iemura *et al.,* 1994; Mekori *et al.,* 1993). SCF has a modest capacity for directly activating mast cells but is usually more active in priming mast cell responses to other stimuli, such as IgE-stimulated mediator release (Columbo *et al.,* 1992; Wershil *et al.,* 1992; Bischoff and Dahinden, 1992). SCF causes the release of small amounts of IL-4 and TNF-α from human lung mast cells (Gibbs *et al.,* 1997). SCF stimulates very late activation antigen-4-mediated cell adhesion to fibronectin and VCAM-1 on human eosinophils (Yuan *et al.,* 1997).

d. ROLE IN ASTHMA. There is very little information on the expression of SCF in asthmatic airways. SCF is expressed in the epithelium of nasal polyps removed from patients with allergic rhinitis (Kim *et al.,* 1997).

D. Inhibitory Cytokines

Although most cytokines initiate, amplify, or perpetuate inflammation, some cytokines appear to have an inhibitory or anti-inflammatory effect on allergic inflammation, either by blocking the expression or effects of inflammatory cytokines or by shifting the immune response away from the Th2 pattern of cytokines (Barnes and Lim, 1998).

1. Interleukin-10.

a. SYNTHESIS AND RELEASE. IL-10, previously known as cytokine synthesis inhibitor factor, was originally identified as a product of murine Th2 clones that suppressed the production of cytokines by Th1 clones responding to antigen stimulation (Fiorentino *et al.,* 1989). In humans, Th0, Th1, and Th2-like $CD4^+$ T cell clones, cytotoxic T cells, activated monocytes, and peripheral blood T cells, including $CD4^+$ and $CD8^+$ T cells, have the capacity to produce IL-10 (Spits and de Waal Malefyt, 1992; Enk and Katz, 1992). Mast cells also have the capacity to produce IL-10. Constitutive IL-10 secretion occurs in healthy lungs, with the major source being alveolar macrophages; however, circulating monocytes appear to be able to secrete more IL-10 than alveolar macrophages (Berkman *et al.,* 1995a).

b. RECEPTORS. The IL-10 receptor is a member of the class II subgroup of cytokine receptors (the IFN receptor family). The IL-10 receptor has been characterized and cloned from a human lymphoma cell line (Liu *et al.,* 1994); it is expressed in several lymphoid and myeloid cell types (Tan *et al.,* 1993) and in natural killer cells (Carson *et al.,* 1995). The IL-10 receptor is highly effective in recruiting the signaling pathways of IL-6-type cytokine receptors, including signal transduction-activated transcription factors 1 and 3 (Lai *et al.,* 1996). The inhibitory effects of IL-10 on monocytes appear to be dependent on NF-κB (Wang *et al.,* 1995).

c. EFFECTS. IL-10 is a pleiotropic cytokine that can exert either immunosuppressive or immunostimulatory effects on a variety of cell types. IL-10 is a potent inhibitor of monocyte/macrophage function, suppressing the production of several proinflammatory cytokines, including TNF-α, IL-1β, IL-6, MIP-1α, and IL-8 (Seitz *et al.,* 1995; de Waal Malefyt *et al.,* 1991a; Fiorentino *et al.,* 1991), although the release of MCP-1 is increased (Seitz *et al.,* 1995). IL-10 inhibits monocyte MHC class II, B7.1/B7.2, and CD23 expression and accessory cell function. Accessory signals mediated by B7 molecules through CD28 on the surface of T cells are essential for T cell activation. Expression of IL-10 by antigen-presenting cells may be an established pathway for the

induction of antigen-specific tolerance, such as that to allergens (de Waal Malefyt *et al.,* 1991b). In contrast, IL-10 up-regulates the monocyte expression of IL-1ra, another anti-inflammatory cytokine (de Waal Malefyt *et al.,* 1992). IL-10 suppresses the synthesis of superoxide anions and NO by activated monocytes/macrophages (Cunha *et al.,* 1992). An anti-IL-10 antibody enhances the release of cytokines from activated monocytes, suggesting that this cytokine may play an inhibitory role when the cell is stimulated (de Waal Malefyt *et al.,* 1991a). IL-10 inhibits the stimulated release of RANTES and IL-8 from human airway smooth muscle cells in culture (John *et al.,* 1997, 1998a). IL-10 inhibits IFN-γ and IL-2 production by Th1 lymphocytes (Fiorentino *et al.,* 1989) and IL-4 and IL-5 production by Th2 cells, by interfering with B7/CD28-dependent signals (Moore *et al.,* 1993; Schandene *et al.,* 1994). IL-10 also inhibits eosinophil survival and IL-4-induced IgE synthesis. On the other hand, IL-10 acts on B cells to enhance their viability, cell proliferation, Ig secretion (with the isotype switch), and class II MHC expression. IL-10 is also a growth co-stimulator for thymocytes and mast cells (Thompson-Snipes *et al.,* 1991), as well as an enhancer of cytotoxic T cell development (Chen and Zlotnik, 1991). IL-10 also activates the transcription of genes for mast-cell derived proteases. IL-10 enhances the production of the tissue inhibitor of metalloproteinases in monocytes and tissue macrophages, while decreasing metalloproteinase biosynthesis (Lacraz *et al.,* 1995).

d. ROLE IN ASTHMA. There is significantly less IL-10 mRNA and protein expressed in alveolar macrophages from asthmatic subjects, compared with those from non-asthmatic individuals (John *et al.,* 1998b; Borish *et al.,* 1996). Triggering of CD23 molecules by anti-CD23 monoclonal antibodies induces IL-10 production by human monocytes (Dugas *et al.,* 1996). An IL-10 polymorphism of the transcription initiation site could be responsible for reduced IL-10 release. Patients with severe asthma are more likely to exhibit polymorphisms in the promoter region that are associated with lower production of IL-10 (Lim *et al.,* 1998). Other studies indicate that inhaled corticosteroid therapy can restore the reduced IL-10 release from macrophages from asthmatic patients (John *et al.,* 1998b), and theophylline also increases IL-10 secretion (Mascali *et al.,* 1996). On the other hand, some studies have indicated that there are increased numbers of macrophages and T cells expressing IL-10 mRNA in bronchoalveolar lavage fluid from patients with asthma (Robinson *et al.,* 1996).

IL-10 inhibits the late response and the influx of eosinophils and lymphocytes after allergen challenge in Brown-Norway rats (Woolley *et al.,* 1994). Coinstillation of IL-10 by the intranasal route significantly inhibits the peritoneal and lung eosinophilia induced by ovalbumin in immunized mice (Zuany Amorim *et al.,* 1995, 1996). Given its anti-inflammatory properties and these effects in animal models of allergic inflammation, IL-10 may have beneficial effects in the treatment of asthma (Pretolani and Goldman, 1997). However, no studies of such effects have been performed. Administration of IL-10 to normal volunteers induced a decrease in circulating $CD2^+$, $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes, with suppression of mitogen-induced T cell proliferation and reduction of TNF-α and IL-1β production from whole blood stimulated with endotoxin ex vivo (Chernoff *et al.,* 1995).

2. Interleukin-1 receptor antagonist. IL-1ra has been isolated from supernatants of monocytes cultured on aggregated Ig or with immune complexes (Arend *et al.,* 1985, 1989), from alveolar macrophages (Galve de Rochemonteix *et al.,* 1990), and from urine of patients with fever or myelomonocytic leukemia (Barak *et al.,* 1986; Seckinger *et al.,* 1990; Balavoine *et al.,* 1986). IL-1ra shares 26 and 19% amino acid homology with IL-1α and IL-1β, respectively. It binds to the IL-1 receptor with affinity similar to that IL-1α or IL-1β (Seckinger *et al.,* 1987), and it inhibits most effects of IL-1 on cells, such as thymocyte proliferation, IL-2 synthesis by T cells, and PGE_2 and collagenase production by fibroblasts (Hannum *et al.,* 1990; Seckinger *et al.,* 1987; Bienkowski *et al.,* 1990; Arend *et al.,* 1990). IL-1ra is preferentially produced by alveolar macrophages, compared with monocytes (Monick *et al.,* 1987), which may underlie the diminished IL-1 bioactivity exhibited by alveolar macrophages, compared with monocytes (Monick *et al.,* 1987; Kern *et al.,* 1988; Wewers *et al.,* 1984). Other IL-1 receptor inhibitors have been described (Muchmore and Decker, 1985; Giri *et al.,* 1990).

IL-1ra blocks proliferation of Th2 but not Th1 clones in vitro (Abbas *et al.,* 1991). Increased expression of IL-1β and IL-1ra in asthmatic airway epithelium has been reported (Sousa *et al.,* 1996). Although the expression of IL-1β is reduced after treatment with inhaled corticosteroids, IL-1ra levels are unchanged, thus shifting the balance away from inflammation (Sousa *et al.,* 1997). In a human airway epithelial cell line, corticosteroids increase the expression of IL-1ra (Levine *et al.,* 1996). In an ovalbumin-sensitized guinea pig model, aerosol administration of IL-1ra immediately before allergen challenge results in protection against bronchial hyperreactivity and accumulation of pulmonary eosinophils (Watson *et al.,* 1993). In a similar model, the late-phase response is inhibited and the number of hypodense eosinophils in bronchoalveolar lavage fluid is decreased (Okada *et al.,* 1995). Trials of IL-1ra in the treatment of asthma are underway.

3. Interferon-γ.

a. SYNTHESIS AND RELEASE. IFN-γ was originally identified as a product of mitogen-stimulated T lymphocytes that inhibited viral replication in fibroblasts. The only known sources of IFN are $CD4^+$ and $CD8^+$ T cells and natural killer cells.

b. RECEPTORS. The IFN-γ receptor is a single transmembrane protein, a member of the cytokine receptor type II superfamily. Although the receptor binds IFN-γ

with high affinity, signal transduction requires a species-specific accessory protein that associates with the extracellular domain of the receptor. The receptor is expressed on T cells, B cells, monocytes/macrophages, dendritic cells, granulocytes, and platelets. Epithelial and endothelial cells also express these receptors.

c. EFFECTS. IFN-γ has extensive and diverse immunoregulatory effects on various cells. It is produced by Th1 cells and exerts an inhibitory effect on Th2 cells (Romagniani, 1990). IFN-γ inhibits antigen-induced eosinophil recruitment in mice (Nakajima *et al.,* 1993). However, IFN-γ may also have proinflammatory effects and may activate airway epithelial cells to release cytokines and express adhesion molecules (Look *et al.,* 1992). IFN-γ has an amplifying effect on the release of TNF-α from alveolar macrophages that is induced by IgE triggering or by endotoxin (Gifford and Lohmann-Matthess, 1987; Gosset *et al.,* 1992), and it increases the expression of class I and class II MHC molecules on macrophages and epithelial cells. IFN-γ is a powerful and relatively specific inhibitor of IL-4-induced IgE and IgG4 synthesis by B cells.

IFN-γ increases the production of IL-1, PAF, and hydrogen peroxide in monocytes, in addition to down-regulating IL-8 mRNA expression, which is up-regulated by IL-2 (Gusella *et al.,* 1993; Sen and Lenggel, 1992; Billiau and Dijkmans, 1990). IFN-γ also synergizes with the effects of TNF-α on the production of RANTES from airway smooth muscle cells (John *et al.,* 1997). On the other hand, IFN-γ inhibits IL-10 production from monocytes (Chomarat *et al.,* 1993), which leads to an up-regulation of TNF-α transcription (Donnelly *et al.,* 1995). Thus, IFN-γ promotes cell-mediated cytotoxic responses while inhibiting allergic inflammation and IgE synthesis. IFN-γ up-regulates class II molecules on monocytes/macrophages and dendritic cells and induces de novo expression on epithelial, endothelial, and other cells, thus making them capable of antigen presentation.

d. ROLE IN ASTHMA. There is evidence for reduced production of IFN-γ by T cells from asthmatic patients, and this correlates with disease severity (Leonard *et al.,* 1997; Koning *et al.,* 1997). This appears to be a feature of atopic disease and is not specific to asthma (Tang *et al.,* 1993). This suggests that defective IFN-γ production may be important in asthma (Halonen and Martinez, 1997), although no polymorphisms of the IFN-γ gene have been associated with asthma (Hayden *et al.,* 1997). Administration of exogenous IFN-γ prevents airway eosinophilia and hyperresponsiveness after allergen exposure in mice (Iwamoto *et al.,* 1993; Lack *et al.,* 1996). Liposome-mediated gene transfer of IFN-γ to the pulmonary epithelium in sensitized mice before secondary antigen exposure also inhibits the pulmonary allergic response (Li *et al.,* 1996). IFN-γ-knock-out mice develop prolonged airway eosinophilia in response to allergen (Coyle *et al.,* 1996). IFN-γ inhibits allergic eosinophilia (Lack *et al.,* 1996; Zuany Amorim *et al.,* 1994) and airway hyperresponsiveness, probably by inducing the formation of IL-10. These studies indicate that IFN-γ has a potential modulating effect on responses to allergen. Allergen immunotherapy of asthmatic patients results in increased production of IFN-γ by circulating T cells (Lack *et al.,* 1997) and in increased numbers of IFN-γ-producing T cells in nasal biopsies (Durham *et al.,* 1996). Corticosteroid treatment also increases IFN-γ expression in asthmatic airways (Bentley *et al.,* 1996), but IFN-γ expression is unexpectedly reduced in corticosteroid-resistant patients (Leung *et al.,* 1995). In asthmatic patients, nebulized IFN-γ reduces the number of eosinophils in bronchoalveolar lavage fluid, indicating its therapeutic potential in asthma (Boguniewicz *et al.,* 1995).

4. Interleukin-12.

a. SYNTHESIS AND RELEASE. IL-12 was initially recognized as a cytokine capable of synergizing with IL-2 to increase cytotoxic T lymphocyte responses, as well as an inducer of IFN-γ synthesis by resting human peripheral blood mononuclear cells in vitro. IL-12 is secreted by antigen-presenting cells, including B lymphocytes and monocytes/macrophages (Trinchieri, 1995; Gately *et al.,* 1998).

b. RECEPTORS. IL-12 receptors are expressed on T cells and natural killer cells. One component of the IL-12 receptor complex is related to gp130 (Chua *et al.,* 1994). The expression of the IL-12 receptor β_2-subunit under the influence of IFN-γ determines the responsiveness of Th1 cells to IL-12 and is of critical importance in Th1/Th2 switching (Rogge *et al.,* 1997).

c. EFFECTS. IL-12 enhances the growth of activated T cells and natural killer cells (Bertagnolli *et al.,* 1992; Perussia *et al.,* 1992; Gately *et al.,* 1991; Robertson *et al.,* 1992) and enhances cytotoxic T cell and natural killer cell activity (Gately *et al.,* 1992; Robertson *et al.,* 1992; Kobayashi *et al.,* 1989). IL-12 stimulates natural killer cells and T cells to produce IFN-γ (Schoenhaut *et al.,* 1992; Wolf *et al.,* 1991; Chan *et al.,* 1991; Kobayashi *et al.,* 1989), promotes in vitro differentiation of mouse and human T cells that secrete IFN-γ and TNF-α (Hsieh *et al.,* 1993; Manetti *et al.,* 1993; Chan *et al.,* 1991; Perussia *et al.,* 1992), and inhibits the differentiation of T cells into IL-4-secreting cells (Hsieh *et al.,* 1993; Manetti *et al.,* 1993). IL-12 indirectly inhibits IL-4-induced human IgE responses by IFN-γ-dependent and -independent mechanisms in vitro (Kiniwa *et al.,* 1992). IL-12 can primarily regulate Th1 cell differentiation, while suppressing the expansion of Th2 cell clones (Manetti *et al.,* 1993), by early priming of undifferentiated Th cells for IFN-γ secretion (Manetti *et al.,* 1994). Therefore, IL-12 may play an important role in directing the development of Th1-like T cell responses against intracellular pathogens, while inhibiting the development of Th2-like responses and IgE synthesis. IL-12 may play an important role in inhibiting inappropriate IgE synthesis and allergic inflammation as a result of allergen exposure.

d. ROLE IN ASTHMA. IL-12 may play an important role in inhibiting inappropriate IgE synthesis and allergic inflammation after allergen exposure. IL-12 treatment of mice during active sensitization reduces antigen-induced influx of eosinophils in bronchoalveolar lavage fluid, inhibits IgE synthesis, and abolishes antigen-induced bronchial hyperresponsiveness (Kips *et al.,* 1996). After an inflammatory response is established, there is inhibition of antigen-induced bronchial hyperresponsiveness and inflammation (Gavett *et al.,* 1995). The effects of IL-12 are largely mediated by IFN-γ (Brusselle *et al.,* 1997). In another study in mice, IL-12 administered at the time of allergic sensitization decreased specific IgE levels, tracheal ring responsiveness to acetylcholine, and eosinophilia in bronchoalveolar lavage fluid after allergen challenge, with IL-5 and IL-10 down-regulation; IL-12 administered after sensitization did not alter specific IgE levels, had little effect on tracheal ring responsiveness, and produced a modest effect on the recruitment of eosinophils, with IL-5 down-regulation but IL-12 up-regulation (Sur *et al.,* 1996). Thus, the effect of IL-12 was dependent on the timing of its administration, in relation to active sensitization.

IL-12 production and IL-12-induced IFN-γ release are reduced in whole-blood cultures from patients with allergic asthma, compared with normal subjects (Van der Pouw Kraan *et al.,* 1997). There is a reduction of IL-12 mRNA expression in airway biopsies from patients with allergic asthma, compared with normal subjects, but after oral corticosteroid treatment the levels of IL-12 mRNA are increased in corticosteroid-sensitive asthmatics, whereas no significant changes are observed in corticosteroid-resistant asthmatics (Naseer *et al.,* 1997). This contrasts with the inhibitory effects of corticosteroids on IL-12 production in human monocytes in vitro (Blotta *et al.,* 1997). Allergen immunotherapy results in an increase in IL-12 expression (Hamid *et al.,* 1997). PGE_2 is a potent inhibitor of human IL-12 production from monocytes (Van der Pouw Kraan *et al.,* 1995). Similarly, β_2-agonists decrease IL-12 production, and this might link regular inhaled β_2-agonist therapy with a worsening of asthma control (Panina-Bordignon *et al.,* 1997).

5. Interleukin-18. IL-18 (IFN-γ-inducing factor) is a cytokine that is a potent inducer of IFN-γ production and plays an important role in Th1 responses (Ushio *et al.,* 1996). Human IL-18 has been cloned from normal human liver cDNA libraries using murine IL-18 cDNA clones. IL-18 is synthesized as a precursor molecule without a signal peptide and requires the IL-1-converting enzyme (caspase-1) for cleavage into a mature peptide.

The human IL-18 receptor has recently been purified and characterized. Human IL-1 receptor protein is a functional IL-18 receptor component (Torigoe *et al.,* 1997).

Recombinant human IL-18 induces IFN-γ production by mitogen-stimulated peripheral blood mononuclear cells, enhances natural killer cell cytotoxicity, increases GM-CSF production, and decreases IL-10 production. IL-18 induces IL-8, MIP-1α, and MCP-1 expression in human peripheral blood mononuclear cells in the absence of any co-stimuli. IL-18 directly stimulates gene expression and synthesis of TNF-α in $CD3^+/CD4^+$ T cells and natural killer cells, with subsequent production of IL-1β and IL-8 in $CD14^+$ monocytes (Puren *et al.,* 1998). IL-18 induces phosphorylation of p56 (*lck*) and MAP kinase, and these may be involved in TCR/CD3-mediated responses (Tsuji Takayama *et al.,* 1997). IL-18 also activates NF-κB in murine Th1 cells for enhancement of IL-2 gene expression by Th1 cells (Matsumoto *et al.,* 1997; Robinson *et al.,* 1997). IL-18, together with IL-12, induces anti-CD40-activated B cells to produce IFN-γ, which inhibits IL-4-dependent IgE production (Yoshimoto *et al.,* 1997).

E. Growth Factors

Chronic asthma is associated with structural remodeling of the airways, with fibrosis (particularly under the epithelium), increased thickness of the airway smooth muscle layer, increased numbers of mucus-secreting cells, and angiogenesis (Redington and Howarth, 1997). These changes are presumably in response to growth factors secreted from inflammatory and structural cells in the airways, and several growth factors have been implicated in asthma.

1. Platelet-derived growth factor.

a. SYNTHESIS AND RELEASE. PDGF is released from many different cells in the airways and consists of two peptide chains, so that AA, BB, or AB dimers may be secreted by different cells. PDGF-A and -B chains are both synthesized as HMW precursors, which are then extensively processed before secretion (Ostman *et al.,* 1988; Bywater *et al.,* 1988). Posttranslational glycosylation and proteolytic cleavage (Bywater *et al.,* 1988; Deuel *et al.,* 1981; Raines and Ross, 1982) both contribute to the heterogeneity in the apparent molecular weights of the mature proteins. Most of the PDGF present in human platelets (from which PDGF was originally isolated) has been identified as AB dimer, although BB and AA dimers also exist (Hart *et al.,* 1990; Hammacher *et al.,* 1988; Heldin, 1988). PDGF-like activity in the conditioned media of various cells, such as those derived from smooth muscle, consists predominantly of the AA dimer (Sejersen *et al.,* 1986). The sources of PDGF include platelets, macrophages, endothelial cells, fibroblasts, airway epithelial cells, and vascular smooth muscle cells. Various stimuli, such as IFN-γ for alveolar macrophages, hypoxia, basic FGF (bFGF), and mechanical stress for endothelial cells, and serum, TNF-α, IL-1, and TGF-β for fibroblasts, can induce PDGF release.

b. RECEPTORS. The PDGF receptors belong to a family of closely related receptor proteins that include the receptor for monocyte-colony stimulating factor and the c-Kit receptor (Yarden *et al.,* 1986). PDGFs exert their actions through a family of at least two classes of PDGF receptors, α and β (Matsui *et al.,* 1989; Hart *et al.,* 1988; Gronwald *et al.,* 1988). These are single-transmembrane domain glycoproteins with an intracellular tyrosine kinase domain (Heldin, 1992). Binding of PDGF dimers induces receptor dimerization, with three possible configurations ($\alpha\alpha$, $\alpha\beta$, and $\beta\beta$). The PDGF receptor α-subunit binds both PDGF A- and B-chains, whereas the receptor β-subunit binds only PDGF B-chains. Therefore, PDGF-AA binds only to PDGF receptor $\alpha\alpha$ dimers, PDGF-AB to receptor $\alpha\alpha$ and $\alpha\beta$ dimers, and PDGF-BB to all three configurations ($\alpha\alpha$, $\alpha\beta$, and $\beta\beta$) (Westermark *et al.,* 1989; Seifert *et al.,* 1989). These receptors are widely distributed on cells of mesenchymal origin, including fibroblasts and smooth muscle cells. Because of their critical role in cell growth, the expression of PDGF receptors is usually tightly controlled. However, receptor levels can be regulated by TGF-β, which can increase the expression of PDGF receptors on human skin fibroblasts (Ishikawa *et al.,* 1990; Bryckaert *et al.,* 1988).

c. EFFECTS. PDGF is a major mitogen, with its primary regulatory role being directed at the cell cycle; it acts as a competence factor, triggering early events of the cell cycle that lead to DNA synthesis and mitosis (Larsson *et al.,* 1989). PDGF induces the expression of competence genes, including the proto-oncogenes c-*myc*, c-*fos*, and c-*jun* (Hall *et al.,* 1989; Greenberg *et al.,* 1986). PDGF may activate fibroblasts to proliferate and secrete collagen (Rose *et al.,* 1986), and it may also stimulate proliferation of airway smooth muscle (Hirst *et al.,* 1992), which is mediated by the α receptor (Hirst *et al.,* 1996). PDGF can be a chemoattractant for connective tissue cells (Grotendorst *et al.,* 1981; Seppa *et al.,* 1982) and can stimulate fibroblasts to contract collagen lattices (Clark *et al.,* 1989).

d. ROLE IN ASTHMA. Levels of PDGF-AA, -AB, and -BB are not increased in asthma, and immunohistochemical analysis of PDGF-AA and -BB and PDGF receptor α- and β-subunits does not reveal increased expression (Chanez *et al.,* 1995). A potential source of PDGF B-chain has been identified as eosinophils in nasal polyps or bronchial biopsies from patients with asthma (Ohno *et al.,* 1995). This, together with their ability to express TGF-β, has raised the possibility that eosinophils are involved in the airway remodeling of asthma.

2. Transforming growth factor-β.

a. SYNTHESIS AND RELEASE. Monocytes constitutively express TGF-β_1 mRNA but release the protein only when activated (Limper *et al.,* 1991; Assoian *et al.,* 1987). Pulmonary macrophages may store large amounts of TGF-β during pulmonary inflammation (Khalil *et al.,* 1989). Lung fibroblasts themselves may be a source of TGF-β (Kelley *et al.,* 1991), but TGF-β is also secreted by inflammatory cells, including eosinophils (Elovic *et al.,* 1994; Ohno *et al.,* 1992), neutrophils (Grotendorst *et al.,* 1989), and airway smooth muscle cells, and structural cells, such as epithelial cells (Sacco *et al.,* 1992). Mast cells may be another source (Pennington *et al.,* 1992). TGF-β is present in the epithelial lining fluid of the normal lower respiratory tract (Yamauchi *et al.,* 1988). TGF-β mRNA and protein have been found to be abundantly expressed in human lung, with TGF-β_1 precursor being immunolocalized throughout the airway wall, including the epithelium and alveolar macrophages, and the mature protein being localized mainly within the connective tissue of the airway wall (Aubert *et al.,* 1994).

b. RECEPTORS. The TGF-β receptor exists in three forms, i.e., high affinity types I and II and low affinity type III (Wang *et al.,* 1991). The high affinity receptors are serine/threonine kinases related to the activin receptor and are thought to associate to mediate signal transduction, probably through serine/threonine phosphorylation. The type II receptor includes β-glycan and endoglin in its structure and does not transduce signals, but it may concentrate TGF-β on the cell surface and present the ligand to the other receptors.

c. EFFECTS. TGF-β comprises a family of growth-modulating cytokines that have an important influence on the turnover of matrix proteins (Moses *et al.,* 1990). They may either inhibit or stimulate proliferation of fibroblasts, depending on the presence of other cytokines. TGF-β induces the transcription of fibronectin, which can function as a chemotactic agent and growth factor for human fibroblasts (Infeld *et al.,* 1992; Ignotz *et al.,* 1986). TGF-β may also be involved in the process of repair of the airway epithelial damage that is characteristic of asthma, because TGF-β is a potent inducer of differentiation for normal epithelial cells (Masui *et al.,* 1986). TGF-β is a potent profibrotic cytokine that stimulates fibroblasts to promote the synthesis and secretion of many proteins of the extracellular matrix (Raghu *et al.,* 1989). TGF-β is also a potent chemoattractant for many cell types, including monocytes, fibroblasts, and mast cells (Gruber *et al.,* 1994; Wahl *et al.,* 1987). TGF-β activates monocytes to produce other cytokines, such as TNF-α, TGF-α, TGF-β, PDGF-B, and IL-1. TGF-β has complex actions in the immune system. In general, TGF-β_1 inhibits both T and B cells. TGF-β inhibits IL-1-dependent lymphocyte proliferation (Schmidt *et al.,* 1982) and blocks IL-2-mediated induction of IL-2 receptors on T cells (Kehrl *et al.,* 1986). TGF-β inhibits proliferation of airway smooth muscle cells (Cohen *et al.,* 1997).

d. ROLE IN ASTHMA. Expression of TGF-β_1 is reported to be similar in lungs from normal and asthmatic subjects. However, greater expression of TGF-β_1 mRNA and protein by eosinophils from asthmatic subjects has been reported, with their expression correlating with the severity of asthma and the degree of subepithelial fibrosis

(Minshall *et al.,* 1997). In another study, TGF-β_1 immunoreactivity was observed in the epithelium and submucosal cells, such as eosinophils and fibroblasts, but expression was greater in biopsies from patients with chronic bronchitis than in those from patients with asthma (Vignola *et al.,* 1997). Release of TGF-β_1 into bronchoalveolar lavage fluid has been observed after segmental allergen challenge (Redington *et al.,* 1997b). The possibility remains that TGF-β (together with PDGF) may be involved in the remodeling process of asthma, although it may also participate in modulating the T cell response.

3. Fibroblast growth factor. FGF represents a family of heparin-binding growth factors consisting of seven polypeptides, including acidic FGF and bFGF (Basilico and Moscatelli, 1992). Acidic FGF and bFGF are potent modulators of cell proliferation, motility, and differentiation. They are found to be associated with the extracellular matrix. A major role for FGF in the induction of angiogenesis has been proposed (Folkman and Klagsbrun, 1987). bFGF induces an invasive phenotype in cultured endothelial cells, enabling them to penetrate the basement membrane in vitro (Mignatti *et al.,* 1989). bFGF induces increased production of proteolytic enzymes, plasminogen activators, and collagenase (Presta *et al.,* 1986; Moscatelli *et al.,* 1986; Mignatti *et al.,* 1989). bFGF binds to heparan sulfate proteoglycans in basement membranes in vivo (Jeanny *et al.,* 1987). In human adult lung, bFGF has been localized to vascular smooth muscle and endothelial cells of blood vessels of the lungs (Cordon Cardo *et al.,* 1990). bFGF has also been detected at high levels in epithelial cells of the trachea and bronchi. bFGF increases expression of the PDGF receptor α-subunit in human airway smooth muscle and therefore indirectly stimulates proliferation (Bonner *et al.,* 1996).

4. Epidermal growth factor. EGF and TGF-α, which do not bind heparin, also stimulate angiogenesis (Kelley, 1990). EGF expression is increased in the epithelium of patients with bronchitis and in the submucosa of patients with asthma (Vignola *et al.,* 1997). EGF increases airway smooth muscle proliferation (Cerutis *et al.,* 1997), and ET-1 potentiates EGF-induced airway smooth muscle proliferation (Panettieri *et al.,* 1996). Increases in the number of blood vessels in asthmatic airways have been described (Li and Wilson, 1997), and these growth factors may be implicated.

5. Insulin-like growth factor. IGF is produced by airway epithelial cells (Cambrey *et al.,* 1995) and is a potent mitogen for airway smooth muscle proliferation (Noveral *et al.,* 1994). IGF appears to mediate the proliferative effect of LTD_4 on airway smooth muscle, at least in rabbits (Cohen *et al.,* 1995). IGF is a potent mitogen and activates MAP kinases in airway smooth muscle (Kelleher *et al.,* 1995).

VII. Chemokines

Chemokines are chemotactic cytokines (8 to 10 kDa) that are involved in attracting leukocytes into tissues (table 3). More than 40 chemokines are now recognized (Luster, 1998). They are divided into families based on their structures. The major groups are CC chemokines (β-chemokines), in which two cysteine residues are adjacent to each other, and CXC chemokines (α-chemokines), in which these residues are separated by another amino acid. The CC chemokines are involved in chemoattraction of eosinophils, monocytes, and T lymphocytes and are therefore of greatest relevance in asthma (Miller and Krangel, 1992a). A third chemokine family (C chemokines), with a single cysteine residue (of which lymphotactin is the first example), and a fourth family (CXXXC family), with three residues separating the two cysteine residues (of which fractaline is an example), have also been described.

A. CC Chemokines

1. Synthesis and metabolism. MIP-1α and MIP-1β were purified from culture media of endotoxin-stimulated mouse macrophages (Wolpe *et al.,* 1988), and their genes can be coordinately expressed after stimulation of T cells (e.g., with anti-CD3), B cells, or monocytes/macrophages (e.g., with lipopolysaccharide) (Berkman *et al.,* 1995b; Lipes *et al.,* 1988; Miller *et al.,* 1989; Zipfel *et al.,* 1989; Obaru *et al.,* 1986). The MIP-1α gene is rapidly induced in human monocytes after adherence to endothelial cells and to other substrates (Sporn *et al.,* 1990). MCP-1 is a monocyte chemoattractant and activating factor and is the best characterized CC chemokine, having been purified and cloned from different sources (Matsushima *et al.,* 1989; Yoshimura *et al.,* 1989a,b,c;

TABLE 3
Chemoattractant effects of chemokines

Chemokine	Eosinophil	T cell	Monocyte	Neutrophil	Others
IL-8	–	–	–	+++	
RANTES	++	Memory T cells	+	–	Natural killer cells
MCP-1	+	+	++	–	Basophils
MCP-3	+	+	+	–	Dendritic cells
MCP-4	++	+	+	–	
MIP-1α	–	$CD8^+$ cells	++		Dendritic cells, natural killer cells
Eotaxin	+++	–	–	–	Basophils
STCP-1	–	Th2 cells	–	–	

STCP-1, stimulated T cell chemoattractant protein-1.

Miller and Krangel, 1992a). Other CC chemokines, I-309, and RANTES, were purified and cloned as products of activated T cells (Chang *et al.,* 1989; Schall *et al.,* 1988; Miller *et al.,* 1989; Miller and Krangel, 1992b). Subtractive hybridization was used to identify genes uniquely expressed in T cells, and this led to the discovery of RANTES cDNA, encoding a polypeptide of 91 amino acids (a 8-kDa secreted protein). RANTES gene is expressed in IL-2-dependent T cell lines. In peripheral blood mononuclear cells, low but detectable levels of RANTES transcripts can be measured in unstimulated cells, and an increase in mRNA levels is observed 5 to 7 days after antigen treatment or phytohemagglutinin stimulation (Schall *et al.,* 1988). HC-14 (now called MCP-2), which was discovered in IFN-γ-stimulated monocytes, has also been isolated from osteosarcoma cell cultures (Van Damme *et al.,* 1992); these cultures also yielded MCP-3, which has been cloned and expressed (Opdenakker *et al.,* 1993; Minty *et al.,* 1993). MCP-4 was also identified in a large-scale sequencing and expression program for the discovery of new chemokines (Berkhout *et al.,* 1997; Uguccioni *et al.,* 1996; Makwana *et al*., 1997). Eotaxin is an unusually selective chemokine that was discovered as an attractant for eosinophils in the bronchoalveolar lavage fluid obtained from an experimental model of allergen exposure of sensitized guinea pigs (Jose *et al.,* 1994) and was subsequently shown to be present in humans (Ponath *et al.,* 1996b). A functionally similar chemokine, eotaxin-2, was recently described (Forssmann *et al.,* 1997). Stimulated T cell chemotactic protein-1 is another newly identified CC chemokine; it is a chemoattractant for Th2 cells (Chang *et al.,* 1997).

In general, monocytes and tissue macrophages are rich sources of CC chemokines, usually associated with de novo synthesis. MCP-1 and MCP-2 are major stimulated products of monocytes. Lymphocytes are sources of some CC chemokines, particularly RANTES (Schall *et al.,* 1988, 1992; Miller *et al.,* 1989), I-309 (Miller *et al.,* 1989, 1990), MIP-1α (Schall *et al.,* 1992; Miller *et al.,* 1989; Zipfel *et al.,* 1989), and MIP-1β (Zipfel *et al.,* 1989; Ziegler *et al.,* 1991). Neutrophils can produce MIP-1α (Kasama *et al.,* 1993). Eosinophils of patients with hypereosinophilic syndrome express mRNA for MIP-1α (Costa *et al.,* 1993). Epithelial cells stimulated with IL-1β or TNF-α produce RANTES (Berkman *et al.,* 1995c) and eotaxin (Lilly *et al.,* 1997) but not MIP-1α. MCP-1, RANTES, and eotaxin immunoreactivity has been reported in human airway epithelium (Berkman *et al.,* 1995c; Sousa *et al.,* 1994). Cultured human airway epithelial cells and cell lines express RANTES and MCP-4 in response to stimulation with proinflammatory cytokines (Berkman *et al.,* 1995c; Kwon *et al.,* 1995; Stellato *et al.,* 1995, 1997). RANTES and eotaxin are also produced by cultured human airway smooth muscle cells (John *et al.,* 1997). MCP-1 and RANTES are produced by human eosinophils (Ying *et al.,* 1996; Izumi *et al.,* 1997).

2. Receptors. The chemokine receptors form a family of structurally and functionally related proteins that are members of the superfamily of G protein-coupled receptors. At least five CC chemokine receptors (CCRs) have been identified, with others being more recently cloned. The known receptors include CCR1, which binds MIP-1α, RANTES, and MCP-3 (Gao *et al.,* 1993; Neote *et al.,* 1993), CCR2, which binds MCP-1 and MCP-3 (Charo *et al.,* 1994; Combadiere *et al.,* 1995), CCR3, which binds eotaxin, RANTES, MCP-3, and MCP-4 (Ponath *et al.,* 1996a), CCR4, which binds MCP-1, MIP-1α, and RANTES (Hoogewerf *et al.,* 1996; Power *et al.,* 1995), and CCR5, which binds MIP-1α, MIP-1β, and RANTES (Raport *et al.,* 1996). Chemokine receptor usage by eosinophils has generated considerable interest, because of the possibility of using receptor antagonists to block eosinophil influx and degranulation in asthma. CCR3 is considered to be the eotaxin receptor mainly mediating chemotaxis and has been identified as being the major CCR on eosinophils and basophils. An antagonistic monoclonal antibody selective for CCR3 inhibits eosinophilia (Heath *et al.,* 1997). Basophils also express CCR3, which mediates chemotaxis. However, the release responses of basophils are mediated by activation of the MCP-1 receptor (CCR2), which is expressed on basophils but not on eosinophils. Eosinophils also express CCR1, which is responsible for the MIP-1α response and part of the RANTES response. CCR5 is not expressed on eosinophils or basophils but is expressed on monocytes, which also express CCR1, CCR2, and CCR4. Several cytokines, including IL-2, IL-4, IL-10, and IL-12, can up-regulate CCR1 and CCR2 in $CD45RO^+$ blood lymphocytes, which is associated with an increase in the chemotactic activity of RANTES and MCP-1 for these cells (Loetscher *et al.,* 1996a).

3. Effects on airways. Chemokines may play a major role in activating migrating leukocytes and endothelial cells to increase adhesiveness and in establishing a chemotactic gradient. MIP-1α that has been immobilized by binding to proteoglycans binds to endothelium to trigger the adhesion of T cells (particularly $CD8^+$ T cells) to VCAM-1 (Choudry *et al.,* 1991). MIP-1α has been localized to lymph node endothelium and could act as a tethered ligand on endothelial cells, thus providing the required signals for activation of lymphocyte integrins for adhesion to endothelium and for migration.

RANTES is a powerful eosinophil chemoattractant, being as effective as C5a and 2 to 3 times more potent than MIP-1α (Kameyoshi *et al.,* 1992; Rot *et al.,* 1992). RANTES up-regulates the expression of CD11b/CD18 on eosinophils (Alam *et al.,* 1993). RANTES and MIP-1α induce exocytosis of eosinophil cationic protein from cytochalasin B-treated cells, although RANTES is relatively weak in this effect (Rot *et al.,* 1992). When injected in the skin of dogs, RANTES induces infiltration of eosinophils and monocytes (Meurer *et al.,* 1993). RANTES, but not MIP-1α, also elicits a respiratory burst from

eosinophils (Rot *et al.,* 1992). MCP-2, MCP-3, and MCP-4 are potent chemoattractants for eosinophils (Uguccioni *et al.,* 1996; Dahinden *et al.,* 1994; Weber *et al.,* 1995; Makwana *et al*., 1997; Minty *et al*., 1993b). Eotaxin and eotaxin-2 have selective chemoattractant activities for eosinophils in vitro and in vivo in the skin (Forssmann *et al.,* 1997). Cooperation between IL-5 and CC chemokines (such as RANTES and eotaxin) is now increasingly recognized, with IL-5 being essential for mobilization of eosinophils from the bone marrow during allergic reactions and for local release of chemokines to induce homing and migration into tissues (Collins *et al.,* 1995; Mould *et al.,* 1997; Rothenberg *et al.,* 1996).

RANTES is a chemoattractant for memory T cells in vitro (Schall *et al.,* 1990). Human MIP-1α and -β are also chemoattractants for distinct subpopulations of lymphocytes, i.e., MIP-1α for $CD8^+$ and MIP-1β for $CD4^+$ T lymphocytes (Schall *et al.,* 1993). RANTES attracts both phenotypes and acts on resting and activated T lymphocytes, whereas MIP-1α and MIP-1β are effective only on anti-CD3-stimulated cells (Taub *et al.,* 1993a). On the other hand, MIP-1β but not MIP-1α has been reported to be chemotactic for resting T cells and enhances the adherence of $CD8^+$ but not $CD4^+$ cells to VCAM-1 (Tanaka *et al.,* 1993). MCP-1, MCP-2, MCP-3, and MCP-4 induce T cell migration (Carr *et al.,* 1994; Loetscher *et al.,* 1994). Natural killer cells migrate vigorously in response to RANTES, MIP-1α, and MCP-1 (Maghazachi *et al.,* 1994; Loetscher *et al.,* 1996). Another CC chemokine, interferon-γ-inducible 10kDa protein, is a chemoattractant for human monocytes and promotes T cell adhesion to endothelial cells (Taub *et al.,* 1993b). The C chemokine lymphotactin also shows T lymphocyte chemoattractant activity (Kelner *et al.,* 1994).

CC chemokines are powerful stimulants of basophils. MCP-1 is as potent as C5a in stimulating exocytosis in human basophils (Bischoff *et al.,* 1992; Alam *et al.,* 1992; Kuna *et al.,* 1992a), with release of high levels of histamine. In the presence of IL-3, IL-5, or GM-CSF, there is enhanced release of histamine and production of LTC_4 (Bischoff *et al.,* 1992; Kuna *et al.,* 1992a). RANTES and MIP-1α are less effective releasers of histamine from basophils. MIP-1α is inactive on basophils (Bischoff *et al.,* 1993). RANTES is the most effective basophil chemoattractant (Alam *et al.,* 1992; Kuna *et al.,* 1992b; Bischoff *et al.,* 1993), whereas MCP-1 is more effective as an inducer of histamine and LT release (Bischoff *et al.,* 1993). Eotaxin-1 and eotaxin-2 also are chemoattractant for basophils, in addition to stimulating release of histamine and LTC_4 (Forssmann *et al.,* 1997).

The CC chemokines MCP-1, RANTES, I-309, MCP-2, and MCP-3 attract monocytes in vitro (Miller and Krangel, 1992b; Sozzani *et al.,* 1991b; Rollins *et al.,* 1991b; Yoshimura *et al.,* 1989b; Schall *et al.,* 1990b; Van Damme *et al.,* 1992), and MCP-1, MCP-2, and MCP-3 induce selective infiltration of monocytes in animal skin (Zachariae *et al.,* 1990; Van Damme *et al.,* 1992). All CC chemokines stimulate intracellular Ca^{2+} release (Miller and Krangel, 1992b; Bischoff *et al.,* 1993b). MCP-1 also induces a respiratory burst, the expression of β_2-integrins (CD11b/CD18 and CD11c/CD18), and the production of IL-1 and IL-6 (Jiang *et al.,* 1992; Zachariae *et al.,* 1990; Rollins *et al.,* 1991). Growth of tumor cell lines cultured in the presence of human blood lymphocytes is inhibited by the addition of MCP-1 (Matsushima *et al.,* 1989). Dendritic cells increase intracellular Ca^{2+} release and migrate in response to MCP-3, MCP-4, MIP-1α, and MIP-5 (Sozzani *et al.,* 1997).

4. Role in asthma. The potential role of chemokines in asthma is supported by observations that many cell types present in asthmatic airways (in particular, monocytes/macrophages, T cells, airway smooth muscle cells, and airway epithelial cells) have the potential to generate chemokines. CC chemokines can be detected in bronchoalveolar lavage fluid, although only at low levels, even after the fluid has been concentrated. Increased levels of MCP-1, RANTES, and MIP-1α in asthmatic patients have been reported, and the eosinophil chemoattractant activity of bronchoalveolar lavage fluid from asthmatics was blocked by antibodies to RANTES and MCP-3 (Alam *et al.,* 1996). The increased levels were not confirmed in other studies (Cruikshank *et al.,* 1995; Fahy *et al.,* 1997). However, the chemokines MIP-1α, MCP-1, and RANTES are elevated in bronchoalveolar lavage fluid after segmental allergen challenge (Holgate *et al.,* 1997; Cruikshank *et al.,* 1995). Using a semiquantitative, reverse transcription-polymerase chain reaction assay, RANTES but not MIP-1α mRNA expression has been shown to be increased in bronchial biopsies from patients with mild asthma (Berkman *et al.,* 1996a). No differences in MIP-1α mRNA expression are observed in alveolar macrophages obtained from normal or asthmatic subjects, but MIP-1α release is increased with alveolar macrophages from asthmatic patients (John *et al.,* 1998b). Increased expression of RANTES and MCP-3 mRNA has been reported in the airway submucosa of patients with allergic and nonallergic asthma (Humbert *et al.,* 1997b). Although RANTES expression in the epithelium of the airway mucosa can be demonstrated by immunohistochemical analysis, there do not appear to be differences between normal and asthmatic subjects. The epithelial expression of RANTES can be inhibited by inhaled corticosteroid therapy (Wang *et al.,* 1996). However, the CC chemokine MCP-1 has been shown to be overexpressed in asthmatic epithelium (Sousa *et al.,* 1994). The chemoattractant activity of bronchoalveolar lavage fluid obtained from patients with seasonal asthma, during the pollen season, was completely suppressed by antibodies to RANTES and IL-5 (Venge *et al.,* 1996). Eotaxin mRNA and protein expression is increased in the airways of asthmatics, mainly in epithelium, T cells, macrophages, and eosinophils (Mattoli *et al.,* 1997; Lamkhioued *et al.,* 1997). In guinea pigs, allergen chal-

lenge induces eotaxin expression mainly in airway epithelium and macrophages (Humbles *et al.,* 1997). Targeted disruption of eotaxin partially reduces antigen-induced tissue eosinophilia in mice (Rothenberg *et al.,* 1997). The availability of specific CCR antagonists, particularly for CCR3, will make it possible to examine the contributions of these chemokines in allergic inflammation and asthma.

B. CXC Chemokines

There are several CXC chemokines, all of which selectively attract neutrophils. IL-8 has been most carefully described and is considered in detail here.

1. Synthesis and metabolism. Platelet factor-4, stored in platelet α-granules, was the first member of the CXC chemokine family to be described. However, IL-8 [also referred to as neutrophil-activating protein (NAP)-1] is the most extensively studied member of the entire chemokine superfamily, with its major actions being as a neutrophil chemoattractant and activator. Several other CXC chemokines that are similar to IL-8 were discovered in rapid succession, including NAP-2 (arising from amino-terminal processing of platelet basic protein) (Walz and Baggiolini, 1990), growth-related oncogene protein (GRO)-α, GRO-β, and GRO-γ (Geiser *et al.,* 1993; Haskill *et al.,* 1990), epithelial cell-derived neutrophil-activating protein (Walz *et al.,* 1991a), and granulocyte chemotactic protein-2 (Proost *et al.,* 1993). A secreted protein produced by lipopolysaccharide-stimulated murine macrophages, termed MIP-2, was found to be a chemoattractant for human neutrophils and to be closely related to GRO-α (Wolpe and Cerami, 1989). In general, monocytes and tissue macrophages are rich sources of CXC chemokines, usually associated with de novo synthesis. Monocytes respond to a wide variety of proinflammatory agents, including IL-1β, TNF, GM-CSF, IL-3, lipopolysaccharide, and immune complexes, to release IL-8. IL-8 has also been induced after adherence of monocytes to plastic and after changes in ambient oxygen levels (Metinko *et al.,* 1992; Kasahara *et al.,* 1991). Eosinophils also release IL-8 after stimulation with the calcium ionophore A23187, but not with TNF-α or IL-1β (Braun *et al.,* 1993). Airway epithelial cells and airway smooth muscle cells stimulated with IL-1β or TNF-α produce IL-8 (John *et al.,* 1998a; Kwon *et al.,* 1994a,b; Standiford *et al.,* 1990a; Elner *et al.,* 1990; Galy and Spits, 1991). IL-8 expression by epithelial cells is increased by respiratory syncytial virus infections (Choi and Jacoby, 1992) and exposure to neutrophil elastase (Nakamura *et al.,* 1992).

Several transcriptional regulatory elements, including NF-KB, NF-IL-6, AP-1, glucocorticoid element, and an octamer-binding motif, can bind to the region preceding the first exon (Mukaida *et al.,* 1989). IL-6 and NF-κB-like factors may act as *cis*-acting elements in IL-8 mRNA expression (Mukaida *et al.,* 1990). IL-8 mRNA expression after stimulation with IL-1β or TNF-α is rapid and results at least partly from transcriptional activation, as shown by nuclear run-on assays (Mukaida *et al.,* 1992; Kwon *et al.,* 1994a; Mukaida and Matsushima, 1992; Sica *et al.,* 1990). A secondary phase of IL-8 mRNA expression, after an early rapid increase induced by IL-1, has been observed with cultured human airway epithelial cells. Enhancement of expression can be induced by cycloheximide, presumably by coinduction of inhibitors of synthesis of negative regulatory elements (Mukaida *et al.,* 1992; Mukaida and Matsushima, 1992). The stability of IL-8 mRNA may be influenced by RNA instability elements (AUUUA) found in the 3′-untranslated region (Shaw and Kamen, 1986; Matsushima *et al.,* 1988). IL-8 expression in blood monocytes (Seitz *et al.,* 1991) and in airway epithelial cells (Kwon *et al.,* 1994b) can be inhibited by glucocorticoids, and IFN-γ, IL-4, and IL-10 can inhibit IL-8 production in blood monocytes (de Waal Malefyt *et al.,* 1991a; Standiford *et al.,* 1990b; Seitz *et al.,* 1991). Most of the effects of glucocorticoids on IL-8 mRNA expression occur through inhibition of transcription (Kwon *et al.,* 1994b).

2. Receptors. Two receptors for IL-8 have been cloned, one of high affinity (IL-8 receptor type 1) and the other of low affinity (IL-8 receptor type 2) (Murphy and Tiffany, 1991; Holmes *et al.,* 1991). These receptors form a family of structurally and functionally related proteins, being members of the superfamily of heptahelical, rhodopsin-like, G protein-coupled receptors. IL-8 also induces G protein activation in neutrophils (Kupper *et al.,* 1992). IL-8 receptor type 1 is specific for IL-8, and other CXC chemokines do not bind to it (Holmes *et al.,* 1991). IL-8 receptor type 1 was cloned from a neutrophil cDNA library that was isolated from cDNA pools by using its ability to confer IL-8 binding sites to COS cells (Holmes *et al.,* 1991); the deduced sequence is 77% identical to that of IL-8 receptor type 2. IL-8 receptor type 2 can be activated by CXC chemokines containing the sequence Glu-Leu-Arg in the amino-terminal domain, including IL-8, the GROs, and NAP-2, but not by CC chemokines (Lee *et al.,* 1992; Murphy and Tiffany, 1991). Neutrophils, basophils, and lymphocytes have been shown to possess functional receptors.

3. Effects on airways. IL-8 is mainly a neutrophil chemoattractant and activator. The chemoattractant activity of IL-8 is potentiated by its binding to heparan sulfate or heparin, although the IL-8-activating activity is reduced (Webb *et al.,* 1993). IL-8 induces shape changes, transient increases in $[Ca^{2+}]_i$, exocytosis (with release of enzymes and proteins from intracellular storage organelles), and respiratory bursts through activation of NADPH oxidase (Baggiolini and Wymann, 1990). IL-8 also up-regulates the expression of two integrins (CD11b/CD18 and CD11c/CD18) during exocytosis of specific granules (Detmers *et al.,* 1990, 1991). IL-8 activates neutrophil 5-LO, with the formation of LTB_4 and 5-HETE (Schroder, 1989), and also induces the production of PAF (Bussolino *et al.,* 1992).

IL-8 can also induce $[Ca^{2+}]_i$ elevations, shape changes, and release of eosinophil peroxidase in eosinophils from patients with hypereosinophilic syndrome (Kernen *et al.,* 1991). IL-8 has weak chemotactic activity for either $CD4^+$ or $CD8^+$ T lymphocytes (Bacon and Camp, 1990), but intradermal injection of IL-8 in humans does not attract lymphocytes (Swensson *et al.,* 1991; Leonard *et al.,* 1991). IL-8 induces the release of histamine (White *et al.,* 1989; Dahinden *et al.,* 1989) and cys-LTs (Dahinden *et al.,* 1989) from human blood basophils, with enhanced release with IL-3, IL-5, or GM-CSF pretreatment (Bischoff *et al.,* 1991). IL-8 induces a small release of intracellular Ca^{2+} and a respiratory burst (Walz *et al.,* 1991b).

4. Role in asthma. An early report showed enhanced coexpression of IL-8 and GM-CSF in bronchial epithelial cells from patients with asthma (Marini *et al.,* 1992). Free IL-8 has been detected in the sera and bronchial tissue of subjects with severe atopic asthma but not in samples from normal subjects or patients with mild atopic asthma, suggesting that IL-8 may be a marker of severe asthma. IL-8 was also found to be complexed with IgA, levels of which were increased in bronchial tissue in asthma (Shute *et al.,* 1997). However, in segmental local challenge studies of patients with allergic asthma, increased IL-8 levels correlated with neutrophil influx (Teran *et al.,* 1996), indicating that IL-8 may be mostly responsible for neutrophil chemotaxis. Enhanced release of IL-8 from alveolar macrophages obtained from patients with mild asthma, compared with those from normal subjects, has been demonstrated (Hallsworth *et al.,* 1994). There is no increase in IL-8 levels in induced sputum for patients with mild asthma, in contrast to the markedly elevated levels for patients with chronic obstructive pulmonary disease and bronchiectasis (Chanez *et al.,* 1996; Keatings *et al.,* 1996). Increased levels of IL-8 have been measured in bronchoalveolar lavage fluid from patients with asthma or bronchitis (Chanez *et al.,* 1996).

IL-8 appears to possess chemotactic activity for primed eosinophils (Warringa *et al.,* 1991). Human IL-8 is able to induce accumulation of guinea pig peritoneal eosinophils in guinea pig skin (Collins *et al.,* 1993), and a human anti-IL-8 antibody inhibited IL-1-induced eosinophil accumulation in rat skin (Sanz *et al.,* 1995). Local instillation of recombinant human IL-8 to the nose can lead to extravascular accumulation of eosinophils in the nasal mucosa of atopic subjects but not normal subjects (Douglass *et al.,* 1994).

VIII. Proteases

Several proteases are secreted in asthma and should therefore be considered as mediators. Proteases may have important effects on airway function in asthma. Mast cell tryptase has been studied in greatest detail, but other proteases that may be secreted in asthma include mast cell chymase and matrix metalloproteinases (MMP) (Caughey, 1997).

A. Synthesis and Metabolism

Tryptase is a trypsin-like serine protease that is the major component of mast cell granules, particularly in mucosal mast cells (which contain ~10 pg/cell). Several tryptase genes have been identified, with β-tryptase predominating over α-tryptase. Tryptase is associated with heparin in mast cell granules and is secreted by exocytosis. Tryptase is secreted as a glycosylated heparin-bound tetramer of ~150 kDa and is relatively stable. Because of its restriction to mast cells and its stability, it has been used as a marker of mast cell degranulation.

Chymase and the related protease cathepsin G are found in the connective tissue type of mast cells and are bound to heparin in mast cell granules. Both have chymotrypsin-like activity. Several MMPs comprise a group of structurally related proteases that are secreted by inflammatory and structural cells. MMP-9 (gelatinase B) is expressed in eosinophils of asthmatic airways (Ohno *et al.,* 1997). Neutrophil elastase, which is a serine protease derived from neutrophils, may also be involved in asthma when neutrophilic inflammation is prominent, such as in severe asthma (Wenzel *et al.,* 1997).

B. Receptors

Little is known regarding the molecular mechanisms of the actions of proteases on cell function. MMPs and neutrophil elastase produce their effects through degradation of matrix proteins, including collagen, elastin, and fibronectin. Tryptase and chymase cleave specific proteins. Chymase also degrades matrix proteins and may activate MMPs by cleaving the active enzyme from an inactive precursor peptide. Some of the effects of tryptase and chymase appear to be mediated by protein-activated receptors that are similar to the thrombin receptor. Tryptase activates protein-activated receptor-2 (Molino *et al.,* 1997; Dery *et al.,* 1998) by cleaving part of the amino-terminal extracellular domain; this reveals sequences that then activate the G protein-coupled receptor, leading to signal transduction.

C. Effects on Airways

1. Airway smooth muscle. Tryptase increases the responsiveness of human airways to histamine in vitro, and this effect is more pronounced in sensitized airways (Johnson and Knox, 1997). Tryptase may also increase bronchoconstriction by degrading the bronchodilating neuropeptides VIP and peptide histidine isoleucine (Tam *et al.,* 1990). Inhaled tryptase causes bronchoconstriction and airway hyperresponsiveness in sheep, effects that are largely mediated by mast cell activation (Molinari *et al.,* 1996). Tryptase also potently degrades CGRP (Tam and Caughey, 1990). Tryptase is a potent

stimulant of airway smooth muscle proliferation (Brown *et al.,* 1995).

2. Other effects. Tryptase and chymase potently induce plasma extravasation in guinea pig skin and thus may contribute to microvascular leakage in asthma (He and Walls, 1997). Chymase, cathepsin G, and neutrophil elastase are potent secretagogues in submucosal glands (Sommerhoff *et al.,* 1989, 1990). Tryptase appears to be chemotactic for eosinophils and may interact with other eosinophil chemotactic factors (Walls *et al.,* 1995).

Tryptase is a potent stimulant of fibroblast proliferation and collagen secretion and appears to act synergistically with other mitogens (Hartmann *et al.,* 1992; Cairns and Walls, 1997). It may therefore play a role in the characteristic subepithelial fibrosis observed in asthmatic airways. Chymase and cathepsin G convert latent TGF-β_1 to its active form, and this may also promote fibrosis. Tryptase is mitogenic for airway epithelial cells and increases the expression of IL-8 and ICAM-1 (Cairns and Walls, 1996).

D. Role in Asthma

1. Release. Increased levels of tryptase have been reported in bronchoalveolar lavage fluid after allergen challenge (Wenzel *et al.,* 1988) and in induced sputum from asthmatic patients (Louis *et al.,* 1997). Increased levels of MMP-9 in bronchoalveolar lavage fluid from asthmatic patients have been reported (Mautino *et al.,* 1997) and are presumably produced by eosinophils and alveolar macrophages, which show increased expression of this enzyme.

2. Effects of inhibitors. The tryptase inhibitor APC 366 inhibits the late response to allergen and airway hyperresponsiveness in sensitized sheep (Clark *et al.,* 1995). Lactoferrin, which disrupts the tetrameric structure of tryptase, has a similar effect (Elrod *et al.,* 1997). In a preliminary report, nebulized APC 366 administered for 4 days produced a small inhibitory effect on the late response to allergen but had no effect on airway hyperresponsiveness to histamine (Krishna *et al.,* 1998). More potent and selective tryptase inhibitors are now in development.

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