

Milestones in the biology and pharmacology of histamine H₁-receptor antagonists

Marone G. Milestones in the biology and pharmacology of histamine H₁-receptor antagonists.
Allergy 1997; 52(suppl 34): 7-13. © Munksgaard 1997.

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Daniele Bovet's pioneering discovery that a series of compounds possessing anti-histamine activity reduced the symptoms of anaphylaxis provided the proof that histamine plays a pivotal role as a mediator of allergic reactions. Basophils and mast cells are the major sources of histamine in man and they are thus one of the primary effector cells of allergic inflammation. Some H₁-receptor antagonists possess a variety of antiinflammatory activity to H₁ antagonism *in vitro* and *in vivo*. This promising area should be explored further and much remains to be done in the evaluation of the immunodulatory effects of anti-histamines.

Key words: basophils; cetirizine; histamine; mast cells.

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Histamine is one of a heterogeneous group of diverse substances released from tissues during injury or inflammatory reactions. These substances include histamine, serotonin, kinins, and various lipid mediators, such as the prostaglandins, leukotrienes, lipoxins, and platelet activating factors (1). Histamine was the first of the substances to be discovered. It was synthesized chemically in 1907 and its biologic activity was discovered in 1910, when it was detected as a uterine stimulant in extracts of ergot.

Histamine became implicated as a mediator of allergic reactions when Dale and Laidlaw found that the effects of histamine mimic those occurring during anaphylaxis (2, 3). In a series of elegant papers Dale and Laidlaw made three general conclusions about histamine. They noted that when applied locally it produces redness, swelling, and edema. Their second observation was that the introduction of histamine into circulation reproduces symptoms that are characteristic of shock. They also noted that in the guinea pig, an animal that is particularly sensitive to histamine, it induced severe bronchoconstriction.

Daniele Bovet's pioneering discovery that a series of compounds possessing anti-histamine activity reduced the symptoms of anaphylaxis provided the definitive proof that histamine plays a pivotal role as a mediator of allergic reactions (4, 5). It was for the identification of anti-histamines that

Daniele Bovet was awarded the Nobel Prize for Physiology and Medicine in 1957. Subsequent studies revealed that after challenge with the specific antigen histamine was actively secreted *in vitro* from cells (peripheral blood basophils and tissue mast cells) that bear high affinity receptors for IgE (FcεRI) (6). In addition, it was demonstrated that histamine released from mast cells and basophils induces the characteristic manifestations of allergic reactions by activating histamine receptors on smooth muscles and blood vessels (7).

Although a pool of non-mast cell-associated histamine exists in such tissues as stomach (8), and perhaps in other tissues, basophils and mast cells are the major sources of histamine in man (9). In general, there appears to be an inverse relationship between the number of mast cells versus basophils in different species: basophils are much more numerous in man than in rat or mouse. The number of basophils in humans is low (approximately $5 \times 10^4/\text{ml}$), whereas the density of mast cells is high in lung parenchyma and lower in the skin, heart and synovial tissues (10-13).

Histamine is rapidly (within 3 to 15 min) released when human mast cells are stimulated by a growing list of immunologic and non-immunologic stimuli (13-15). There is marked heterogeneity in the response to different immunologic (Table 1) and non-immunologic stimuli (Table 2) between mast cells and basophils and among human mast cells

Table 1. Pattern of activation of human basophils and mast cells by immunologic stimuli

	Basophils	HLMC	HSMC	HHMC
<i>Immunologic</i>				
<i>IgE-mediated</i>				
Antigen	++	+	+	+
Anti-IgE	++	+	+	+
Anti-FcεR1	++	+	+	+
Protein A	++	—	—	—
Protein L	++	+	+	+
Protein Fv	++	+	+	+
HRF	+	—	—	—
<i>Non IgE-mediated</i>				
C5a	+	—	+	+
IL-3	+	—	—	—
Stem Cell Factor	—	+	+	+
TNF-α	—	—	+	—
ECP	—	—	—	+
MBP	+	—	—	+
MCP-2	+	—	—	—
MCP-3	+	—	—	—
MCP-4	+	—	—	—
MIP-1α	+	—	—	—

Abbreviations: HLMC: human lung mast cell; HRF: IgE-dependent histamine releasing factor; HSMC: human skin mast cell; HHMC: human heart mast cell; ECP: eosinophil cationic protein; MBP: major basic protein; MCP-2: monocyte chemotactic protein 2; MCP-3: monocyte chemotactic protein 3; MCP-4: monocyte chemotactic protein 4; MIP-1α: macrophage inflammatory protein 1α.

isolated from different anatomic sites. Histamine secretion also occurs during human basophil degranulation (16). The diverse patterns of human basophil and mast cell degranulation are described in detail in the chapter below by Ann M. Dvorak (17).

Another important breakthrough in this area was the identification of histamine H_1 receptors in 1966 by Ash and Schild (18). They proposed the name H_1 for receptors blocked by known antihistamines. They presented evidence that the actions of histamine not blocked by the classic antihistamines, i.e. stimulation of gastric secretion, inhibition of uterus contraction and stimulation of isolated atria, were mediated through a second type of receptor. Since specific antagonists of the second type of histamine receptors were not available, these receptors were left unclassified until the important discovery by Black and his co-workers in 1972 of the histamine H_2 receptor and specific antagonists (19). The existence of two types of receptors, H_1 and H_2 , was thus established. Although H_2 receptors are mainly responsible for the control of gastric acid secretion, there is ample evidence that H_1 and/or H_2 receptors exist among T-lymphocyte subsets, B-cells, monocytes and leukocyte populations (20–26). Another important breakthrough in the field of histamine receptors was the identification of H_3 receptors by Schwartz and his

Table 2. Pattern of activation of human basophils and mast cells by non-immunologic stimuli

	Basophils	HLMC	HSMC	HHMC
<i>Non-Immunologic</i>				
A23187	++	+	+	+
48/80	—	+	+	+
Substance P	—	—	+	—
VIP	—	—	+	—
Pepstatin A	+	—	—	—
f-met peptide	+	—	—	—
PAF	+	—	—	—
Protamine	+	—	+	+
Radio Contrast Media	+	+	—	+
General Anesthetics	—	+	+	+
Morphine	—	—	+	—
Maitotoxin	+	+	+	+
TPA	+	—	—	—
Bryostatin 1, 2 and 5	+	—	—	—

Abbreviations: f-met peptide: formyl-L-leucyl-L-phenylalanine; HLMC: human lung mast cell; HSMC: human skin mast cell; HHMC: human heart mast cell; PAF: platelet-activating factor; TPA: tetradecanoylphorbol-acetate.

co-workers (27); stimulation of H_3 receptors may exert negative modulator effects in the nervous (27) and in the cardiovascular systems (28, 29). A human histamine H_1 receptor has been cloned (30) and this approach could be useful for the molecular analysis of possible histamine H_1 receptor subtypes. Moreover, a gene that encodes the histamine H_2 receptor has been cloned (31).

H_1 receptor antagonists include a large number of compounds with different pharmacokinetics and pharmacodynamic properties (32). The first generation of H_1 receptor antagonists, i.e., chlorpheniramine, diphenhydramine, hydroxyzine and promethazine, became available in the 40s and some of them are still in use. Among the second-generation antihistamines are terfenadine, astemizole, cetirizine, loratadine, ketotifen, azelastine, levocabastine and ebastine, all of which are highly selective for H_1 receptors. First-generation H_1 -receptor antagonists also activate muscarinic cholinergic, 5-hydroxy tryptamine (serotonin), and α -adrenergic receptors, whereas few of the second-generation H_1 antagonists have any of these properties (33). The selectivity of second-generation antagonists reduces their adverse effects on the central nervous system (sedation). The binding of second-generation H_1 antagonist is readily reversible, but some of them such as astemizole, do not readily dissociate from H_1 receptors (32).

Role of histamine and antihistamines in inflammatory and immune responses

The central role of histamine as a mediator of allergic reactions is unchallenged. Recently, other

potentially important effects of histamine on the multifaceted process of inflammation have been defined. Histamine-containing cells (basophils) can be attracted to several types of immunologically mediated inflammatory sites, and then release histamine in response to multiple triggers (10-15). For instance, basophils can be found at the site of inflammation during late-phase reactions in human skin (34) and in lung parenchyma (35) in some cases of bronchial asthma (36-39). Moreover, histamine by interaction with histamine H₂ receptors, generally induces an inhibitory signal to lymphocytes (20, 22, 26), basophils (21) and eosinophils (40), which participate in inflammatory reactions (1). Thus, histamine is an endogenous mediator which might function as a physiologic modulator of inflammation.

Although there is increasing evidence that some H₁ receptor antagonists possess a variety of anti-inflammatory activities beyond H₁ antagonism (41-43), H₁ antihistamines have so far been thought to possess a modest clinical efficacy in human immediate hypersensitivity reactions like bronchial asthma (44-47) and anaphylaxis (48). The low clinical efficacy of H₁ antihistamines may be due to various factors: 1) the local tissue level of histamine is too high to be blocked by clinically obtained tissue levels of antihistamines; 2) mediators other than histamine, such as peptide leukotrienes, PAF, neutral proteases and phospholipase A₂, are important in the pathogenesis of these disorders; 3) histamine's actions are mediated by both H₁ and H₂ receptors, and blockade of both is necessary for therapeutic effects. Although there is evidence in favor of all three of these hypotheses, the role of histamine and antihistamines as important immunomodulatory agents has yet to be clarified. Certainly, the finding of multiple, potent *in vitro* effects of histamine on inflammatory effector cells argues that some of these effects do occur in response to endogenous histamine *in vivo*. Moreover, the multiple *in vitro* and *in vivo* anti-inflammatory effects of some H₁ receptor antagonists, particularly of cetirizine (42, 43, 49-52) might occur in response to therapeutic antihistamine treatment *in vivo*.

Activity of H₁-receptor antagonists

It has been known since 1975 that high concentrations of first-generation antihistamines inhibit histamine release from human basophils (53). The mechanisms by which first-generation H₁ antagonists inhibit mediator release presumably do not involve H₁ receptor antagonism. There is increasing evidence that certain second-generation H₁ antagonists, such as cetirizine, prevent *in vivo* the

release not only of histamine, but also of other mediators of inflammation from human inflammatory cells (50). Cetirizine exerts antiinflammatory activity on human eosinophils (49), neutrophils (54), basophils and mast cells (55). Moreover, cetirizine exerts antiinflammatory effects in patients with allergic disorders (34, 50). Lastly, it has been suggested that cetirizine could modulate ICAM-1 expression on epithelial cells (42). The antiinflammatory activities of second-generation H₁ antagonists are dealt with in detail in the article of Ernest Charlesworth (56).

It is important to emphasize that not all second-generation H₁ antagonists possess antiinflammatory activity, which raises the possibility that the heterogeneity of the antiinflammatory effects is mediated by the activation of isoforms of H₁ receptors or subtypes of H₁ receptors.

The demonstration of the presence and secretion of several cytokines in human basophils (57), eosinophils (58-60), and mast cells (61-63) suggests that experiments be performed to investigate the effect of second-generation H₁ antagonists on cytokine synthesis and release by human inflammatory cells.

Efficacy of H₁-receptor antagonists

Second-generation H₁ antagonists prevent and relieve the symptoms (sneezing, nasal and ocular itching, rhinorrhea, tearing, and conjunctival erythema) of allergic rhino-conjunctivitis if used regularly during the pollen season (64, 65). Second-generation H₁ antagonists relieve pruritus and reduce the number, size and duration of urticarial lesions in patients with chronic urticaria (66, 67). Interestingly in some patients with chronic urticaria refractory to treatment with an H₁ antagonist alone, concurrent treatment with an H₂ antagonist such as cimetidine or ranitidine brings additional relief of the symptoms (68, 69).

The use of second-generation H₁ antagonists in the treatment of patients with bronchial asthma is still under evaluation. First-generation H₁ antagonists were originally contraindicated in patients with asthma because they reduced the viscosity of mucous secretion (44-47). There is now evidence that some of the newer antihistamines may be useful in the treatment of asthma. Grant and co-workers have recently demonstrated that cetirizine given concomitantly with antiasthmatic drugs in patients with bronchial asthma and allergic rhinitis may relieve some of the symptoms (70). This important observation raises the possibility that some second-generation H₁ antagonists may relieve mild symptoms of bronchial asthma. In this volume Malick and Grant review the history of research on antihistamine use in asthma (71).

The use of second-generation H_1 antagonists in patients with atopic dermatitis has not been adequately studied (72, 73). Atopic dermatitis is a very heterogeneous disease whose pathogenesis and clinical manifestations vary according also to the age of patients. Basophil infiltration occurs at the site of skin inflammation in patients with atopic dermatitis (35) suggesting that the release of pro-inflammatory mediators from these cells plays a role in this disorder. We have demonstrated that "spontaneous" and immunologically-mediated basophil releasability of young patients with atopic dermatitis is increased compared to controls of matched ages (74). Early clinical studies aimed at evaluating the efficacy of H_1 receptor antagonists in patients with atopic dermatitis were controversial (72, 73). Trials using the newer H_1 -receptor antagonists in the early phases of atopic dermatitis are still underway.

Another important area of investigation is the use of second-generation H_1 antagonists in the prevention and treatment of anaphylactic and anaphylactoid reactions. H_1 antagonists are useful in the ancillary treatment of anaphylaxis (48) and are given prophylactically concurrently with H_2 antagonists for anaphylactoid reactions to radio contrast media (75, 76). Unfortunately, some of the newer H_1 antagonists (terfenadine and astemizole) are poorly soluble in water and are not available for parenteral use. Considering the relevant cardiovascular effects of some H_1 antagonists (77–79) and the major involvement of the cardiovascular system in systemic anaphylaxis (13, 14, 80–82), it may be more appropriate to use H_1 -antagonists such as cetirizine that are devoid of significant cardiovascular effects in patients at risk of anaphylactic or anaphylactoid reactions.

Safety and adverse effects of H_1 -receptor antagonists

Since H_1 -receptor antagonists are used to treat non-life-threatening disorders, their risk/benefit reaction should be very carefully evaluated in children and in adults. Second-generation H_1 -antagonists have fewer adverse central nervous system effects (e.g. sedation) than first-generation agents. However, when the recommended doses of second-generation H_1 -antagonists are exceeded, central nervous system function may become impaired (83, 84). Moreover, different tests (driving tests, psychomotor, subjective and instrumental) have been used to evaluate the sedative effects of H_1 -antagonists thus explaining some of the controversial results.

Another important topic concerns the catastrophic cardiovascular events that have, on rare

occasions, been associated with the use of H_1 -antagonists. This topic is extensively reviewed by Genovese and Spadaro in this volume (85). However, it is important to remember that histamine H_1 -, H_2 - and H_3 -receptors are present in the human cardiovascular system (29, 80, 81, 86). In addition, the cardiovascular effects of histamine may vary in different pathological conditions (86), and the histamine content of heart tissue of patients with dilated cardiomyopathy was increased when compared to subjects without cardiovascular disease who died in car accidents (87). Moreover, the release of histamine was significantly higher in human heart mast cells from cardiomyopathy patients than controls (87). Thus, the higher cardiac mast cell density and the greater release of their vasoactive mediators in cardiomyopathy and the increased sensitivity of the H_1 -receptors in some patients with unstable angina (80, 81) might suggest that those patients are at increased risk to the cardiac effects of some H_1 -receptor antagonists. Interestingly the prolongation of the QT_c interval has been associated with the use of some (astemizole and terfenadine) but not with other (cetirizine) H_1 -antagonists (77–79, 88). The heterogeneity of the cardiac effects of H_1 -antagonists may be explained by the possible existence of H_1 -receptor subtypes (30).

A final area of interest concerns the effects of H_1 -antagonists on cancer growth. This apparently surprising effect may be due to the interference of the angiogenetic properties of histamine and other mast cell-derived mediators. This fascinating topic has been extensively reviewed by Cynthia J. Meininger in a recent chapter devoted to mast cells and tumor-associated angiogenesis (89). In brief, histamine has been reported to be angiogenic *in vivo* (90, 91) and mitogenic for capillary endothelial cells *in vitro* (92, 93). However, a mechanism of the action of histamine and the possible interference of H_1 receptor antagonists in tumor angiogenesis has not yet been fully elucidated.

Future trends

Interest in the pharmacology and use of H_1 -receptor antagonists has increased over recent years with the introduction of second-generation H_1 -antagonists. Although histamine is not the only endogenous mediator of allergic inflammation, some H_1 antagonists have demonstrated unexpected anti-inflammatory effects *in vivo* and *in vitro*. This promising and fascinating area should be explored further and much remains to be done in the evaluation of the immunomodulatory effects of newer antihistamines. Research in this area will also contribute to define better able to the

physiological role of histamine in the upper and lower respiratory tract (70), in the cardiovascular system (29, 81), in the brain (33) and possibly in cancer growth (89). Newer H₁ antagonists will also be useful to settle the still controversial issue of the use of antihistamines in the treatment of bronchial asthma. The novel finding that some of the newer H₁ antagonists may be useful in the treatment of some patients with asthma (70) is fascinating and certainly warrants additional studies. It is also necessary to understand the difference in efficacy in relation to different pathophysiologic aspects of bronchial asthma in patients of different ages and with different degrees of involvement of bronchial asthma.

The use of newer H₁ antagonists in association with H₂ antagonists should also be evaluated in the prevention or ancillary treatment of anaphylactic/anaphylactoid reactions. In particular, second-generation H₁ antagonists without cardiovascular effects, such as cetirizine, should be included in clinical trials aimed at evaluating their efficacy in the prevention or treatment of anaphylactic/anaphylactoid reactions.

Finally, the safety of new H₁-antagonists introduced into clinical practice should be a prime consideration given their different effects, particularly during pregnancy (94) and in patients with cardiovascular disease (80–82, 86, 87).

In conclusion, despite the wealth of data on the biochemistry and pharmacology of second-generation H₁-antagonists, additional studies need to be performed to understand better the pathophysiologic role of histamine and its role in the control of inflammatory and immune responses in man.

References

- Marone G. Human basophils and mast cells. Biological Aspects. Basel, Karger, 1995.
- Dale HH, Laidlaw PP. The physiological action of β -imidazolyl-ethylamine. J Physiol 1910;41:318-44.
- Dale HH, Laidlaw PP. Histamine shock. J Physiol 1919; 52:355-90.
- Bovet D, Staub AM. Action protectrice des éthers phénoliques au cours de l'intoxication histaminique. Compt Rend Soc Biol 1937;124:547-9.
- Staub AM, Bovet D. Action de la thymoxyéthyl-diéthylamine (929 F) et des éthers phénoliques sur le choc anaphylactique du cobaye. Compt Rend Soc Biol 1937; 125:818-23.
- Lichtenstein LM, Osler AG. Studies on the mechanisms of hypersensitivity phenomena. XII. An *in vitro* study of the reaction between ragweed pollen antigen, allergic human serum and ragweed-sensitive human leukocytes. J Immunol 1966;96:169-79.
- Plaut M, Lichtenstein LM. Histamine, 5-hydroxytryptamine, SRS-A: Discussion of type I hypersensitivity (anaphylaxis). In: Vane JR, Ferreira SH, eds. Handbook of Experimental Pharmacology. Vol. 50/I. Inflammation. New York: Springer Verlag, 1978;345-73.
- Kahlon G, Rosengren E. New approaches to the physiology of histamine. Physiol Rev 1968;48:155-96.
- Marone G. The role of basophils and mast cells in the pathogenesis of pulmonary diseases. Int Archs Allergy Appl Immunol 1985;76 (suppl. 1):70-82.
- Casolaro V, Galeone D, Giacommo A, Sanduzzi A, Melillo G, Marone G. Human basophil/mast cell releasability. V. Functional comparisons of cells obtained from peripheral blood, lung parenchyma and from bronchoalveolar lavage in asthmatics. Am Rev Respir Dis 1989; 139:1375-82.
- De Paulis A, Stellato C, Cirillo R, Ciccirelli A, Oriente A, Marone G. Anti-inflammatory effect of FK-506 on human skin mast cells. J Invest Dermatol 1992;99:723-8.
- De Paulis A, Marinò I, Ciccirelli A, De Crescenzo G, Concardi M, Verga L, et al. Human synovial mast cells. I. Ultrastructure *in situ* and *in vitro* immunologic characterization. Arthritis Rheum 1996;39:1222-33.
- Patella V, Marinò I, Lamparter B, Arbustini E, Adt M, Marone G. Human heart mast cells. Isolation, purification, ultrastructure, and immunologic characterization. J Immunol 1995;154:2855-65.
- Patella V, Bouvet J-P, Marone G. Protein Fv produced during viral hepatitis is a novel activator of human basophils and mast cells. J Immunol 1993;151:5685-98.
- Patella V, De Crescenzo G, Marinò I, Genovese A, Adt M, Gleich GJ, et al. Eosinophil granule proteins activate human heart mast cells. J Immunol 1996;157:1219-25.
- Casolaro V, Spadaro G, Patella V, Marone G. *In vivo* characterization of the anti-inflammatory effect of cyclosporin A on human basophils. J Immunol 1993;151: 5563-73.
- Dvorak AM. Ultrastructural localization of histamine in human basophils and mast cells; changes associated with anaphylactic degranulation and recovery demonstrated with a diamine oxidase-gold probe. Allergy 1997;52:12-22.
- Ash ASF, Schild HO. Receptors mediating some actions of histamine. Br J Pharmacol 1966;27:427-39.
- Black JW, Duncan WAM, Durant CJ, Ganellin CR, Parsons EM. Definition and antagonism of histamine H₂-receptors. Nature 1972;236:385-90.
- Roszkowski W, Plaut M, Lichtenstein LM. Selective display of histamine receptors on lymphocytes. Science 1977; 195:683-5.
- Lichtenstein LM, Gillespie E. Inhibition of histamine release by histamine controlled by H₂ receptor. Nature 1973;244:287-8.
- Rocklin RE, Haberek-Davidson A. Histamine activates suppressor cells *in vitro* using a coculture technique. J Clin Immunol 1981;1:73-9.
- Osband ME, Cohen EB, Miller BR, Shen Y-J, Cohen L, Flescher L, et al. Biochemical analysis of specific histamine H₁ and H₂ receptors on lymphocytes. Blood 1981;58:87-90.
- Cameron W, Doyle K, Rocklin RE. Histamine type I (H₁) receptor radioligand binding studies on normal T cell subsets, B cells, and monocytes. J Immunol 1986;136: 2116-20.
- Villemain FM, Bach J-F, Chatenoud LM. Characterization of histamine H₁ binding sites on human T lymphocytes by means of ¹²⁵I-Iodobolpyramine. Preferential expression of H₁ receptors on CD8 T lymphocytes. J Immunol 1990; 144:1449-54.
- Vannier E, Miller LC, Dinarello CA. Histamine suppresses gene expression and synthesis of tumor necrosis factor α via histamine H₂ receptors. J Exp Med 1991;174:281-4.
- Arrang J-M, Garbarg M, Schwartz J-C. Auto-inhibition of

- brain histamine release mediated by a novel class (H_3) of histamine receptor. *Nature* 1983;302:832-7.
28. Endou M, Poli E, Levi R. Histamine H_3 -receptor signaling in the heart: possible involvement of Gi/Go proteins and N-type Ca^{++} channels. *J Pharmacol Exp Ther* 1994;269:221-9.
 29. Imamura M, Seyedi N, Lander HM, Levi R. Functional identification of histamine H_3 -receptors in human heart. *Circ Res* 1995;77:206-10.
 30. De Backer MD, Gommeren W, Moereels H, Nobels G, Van Gompel P, Leysen JE, et al. Genomic cloning, heterologous expression and pharmacological characterization of a human histamine H_1 receptor. *Biochem Biophys Res Com* 1993;197:1601-8.
 31. Gantz I, Schäffer M, Del Valle J, Logsdon C, Campbell V, Uhler M, et al. Molecular cloning of a gene encoding the histamine H_2 receptor. *Proc Natl Acad Sci USA* 1991;88:429-33.
 32. Simons FER, Simons KJ. The pharmacology and use of H_1 -receptor-antagonist drugs. *N Eng J Med* 1994;330:1663-70.
 33. Snowman AM, Snyder SH. Cetirizine: actions on neurotransmitter receptors. *J Allergy Clin Immunol* 1990;86:1025-8.
 34. Charlesworth EN, Massey WA, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Effect of H_1 receptor blockade on the early and late response to cutaneous allergen challenge. *J Pharmacol Exp Ther* 1992;262:964-70.
 35. Mitchell EB, Chapman MD, Pope FM, Crow J, Jouhal SS, Platts-Mills TAE. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1982;1:127-30.
 36. Liu MC, Hubbard WC, Proud D, Stealey BA, Galli SJ, Kagey-Sobotka A, et al. Immediate and late inflammatory responses to ragweed antigen challenge of the peripheral airways in allergic asthmatics. *Am Rev Respir Dis* 1991;144:51-8.
 37. Kimura I, Moritani Y, Tanizaki Y. Basophils in bronchial asthma with reference to reagin-type allergy. *Clin Allergy* 1973;3:195-202.
 38. Koshino T, Teshima S, Fukushima N, Takaishi T, Hirai K, Miyamoto Y, et al. Identification of basophils by immunohistochemistry in the airways of post-mortem cases of fatal asthma. *Clin Exp Allergy* 1993;23:919-25.
 39. Sparrow D, O'Connor GT, Rosner B, Weiss S. Predictors of longitudinal change in methacholine airway responsiveness among middle-aged and older men: the normative aging study. *Am J Respir Crit Care Med* 1994;149:376-81.
 40. Clark RAF, Gallin JI, Kaplan AP. The selective eosinophil chemotactic activity of histamine. *J Exp Med* 1975;142:1462-76.
 41. Massey WA, Lichtenstein LM. The effects of antihistamines beyond H_1 antagonism in allergic inflammation. *J Allergy Clin Immunol* 1990;86:1019-24.
 42. Ciprandi G, Buscaglia S, Pesce G, Passalacqua G, Rihoux JP, Bagnasco M, et al. Cetirizine reduces inflammatory cell recruitment and ICAM-1 (or CD54) expression on conjunctival epithelium in both early- and late-phase reactions after allergen-specific challenge. *J Allergy Clin Immunol* 1995;95:612-21.
 43. Fasce L, Ciprandi G, Pronzato C, Cozzani S, Tosca MA, Grimaldi I, et al. Cetirizine reduces ICAM-I on epithelial cells during nasal minimal persistent inflammation in asymptomatic children with mite-allergic asthma. *Int Arch Allergy Immunol* 1996;109:272-6.
 44. Holgate ST, Finnerty JP. Antihistamines in asthma. *J Allergy Clin Immunol* 1989;83:537-47.
 45. Dirksen A, Engel T, Frolund L, Heinig JH, Svendsen UG, Weeke B. Effect of a non-sedative antihistaminic (loratadine) in moderate asthma. A double-blind controlled clinical crossover trial. *Allergy* 1989;44:566-71.
 46. Rafferty PP, Jackson L, Smith R, Holgate ST. Terfenadine, a potent histamine H_1 -receptor antagonist in the treatment of grass pollen sensitive asthma. *Br J Clin Pharmacol* 1990;30:229-35.
 47. Bousquet J, Godard P, Michel FB. Antihistamines in the treatment of asthma. *Eur Respir J* 1992;5:1137-42.
 48. Bochner BS, Lichtenstein LM. Anaphylaxis. *N Engl J Med* 1991;324:1785-90.
 49. Fadel R, Herpin-Richard N, Rihoux JP, Henoco E. Inhibitory effect of cetirizine 2HCl on eosinophil migration *in vivo*. *Clin Allergy* 1987;17:373-9.
 50. Charlesworth EN, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Effect of cetirizine on mast cell-mediator release and cellular traffic during the cutaneous late-phase reaction. *J Allergy Clin Immunol* 1989;83:905-12.
 51. Varney V, Gaga M, Frew AJ, De Vos C, Kay AB. The effect of a single oral dose of prednisolone or cetirizine on inflammatory cells infiltrating allergen-induced cutaneous late-phase reactions in atopic subjects. *Clin Exp Allergy* 1992;22:43-9.
 52. Jinquan T, Reimert CM, Deleuran B, Zachariae C, Simonsen C, Thestrup-Pedersen K. Cetirizine inhibits the *in vitro* and *ex vivo* chemotactic response of T lymphocytes and monocytes. *J Allergy Clin Immunol* 1995;95:979-86.
 53. Lichtenstein LM, Gillespie E. The effects of the H_1 and H_2 antihistamines on 'allergic' histamine release and its inhibition by histamine. *J Pharmacol Exp Ther* 1975;192:441-50.
 54. Köller M, Hilger RA, Rihoux JP, König W. Cetirizine exerts anti-inflammatory effects on human neutrophils. *Int Arch Allergy Immunol* 1996;110:52-6.
 55. Okayama Y, Benyon RC, Lowman MA, Church MK. *In vitro* effects of H_1 -antihistamines on histamine and PGD_2 release from mast cells of human lung, tonsil, and skin. *Allergy* 1994;49:246-53.
 56. Charlesworth EN. The role of basophils and mast cells in acute and late phase reactions in the skin. *Allergy* 1997;52:29-41.
 57. Brunner T, Heusser CH, Dahinden CA. Human peripheral blood basophils primed by interleukin 3 (IL-3) produce IL-4 in response to immunoglobulin E receptor stimulation. *J Exp Med* 1993;177:605-11.
 58. Dubucquoi S, Desreumaux P, Janin A, Klein O, Goldman M, Tavernier J, et al. Interleukin 5 synthesis by eosinophils: association with granules and immunoglobulin-dependent secretion. *J Exp Med* 1994;179:703-8.
 59. Moqbel R, Ying S, Barkans J, Newman TM, Kimmit P, Wakelin M, et al. Identification of messenger RNA for IL-4 in human eosinophils with granule localization and release of the translated product. *J Immunol* 1995;155:4939-47.
 60. Lim KG, Wan H-C, Bozza PT, Resnick MB, Wong DTW, Cruikshank WW, et al. Human eosinophils elaborate the lymphocyte chemoattractants IL-16 (lymphocyte chemoattractant factor) and RANTES. *J Immunol* 1996;156:2566-70.
 61. Ohkawara Y, Yamauchi K, Tanno Y, Tamura G, Ohtani H, Nagura H, et al. Human lung mast cells and pulmonary macrophages produce tumor necrosis factor- α in sensitized lung tissue after IgE receptor triggering. *Am J Respir Cell Mol Biol* 1992;7:385-92.
 62. Bradding P, Roberts JA, Britten KM, Montefort S, Djukanovic R, Mueller R, et al. Interleukin-4, -5, and -6 and tumor necrosis factor- α in normal and asthmatic airways: evidence for the human mast cell as a source of these cytokines. *Am J Respir Cell Mol Biol* 1994;10:471-80.

63. Okayama Y, Petit-Frère C, Kassel O, Semper A, Quint D, Tunon-De-Lara MJ, et al. IgE-dependent expression of mRNA for IL-4 and IL-5 in human lung mast cells. *J Immunol* 1995;155:1796-1808.
64. Del Carpio J, Kabbash L, Turenne Y, Prevost M, Hebert J, Bedard PM, et al. Efficacy and safety of loratadine (10 mg once daily), terfenadine (60 mg twice daily), and placebo in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1989;84:741-6.
65. Falliers CJ, Brandon ML, Buchman E, Connel JT, Dockhorn R, Leese PT, et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. *Ann Allergy* 1991;66:257-62.
66. Juhlin L, Arendt C. Treatment of chronic urticaria with cetirizine dihydrochloride a non-sedating antihistamine. *Br J Dermatol* 1988;119:67-71.
67. Belaich S, Bruttman G, DeGreef H, Lachapelle JM, Paul E, Pedrali P, et al. Comparative effects of loratadine and terfenadine in the treatment of chronic idiopathic urticaria. *Ann Allergy* 1990;64:191-4.
68. Paul E, Bödeker RH. Treatment of chronic urticaria with terfenadine and ranitidine: a randomized double-blind study in 45 patients. *Eur J Clin Pharmacol* 1986;31:277-80.
69. Bleehen SS, Thomas SE, Greaves MW, Newton J, Kennedy CTC, Hindley F, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. *Br J Dermatol* 1987;117:81-8.
70. Grant JA, Nicodemus CF, Findlay SR, Glovsky MM, Grossman J, Kaiser H, et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1995;95:923-32.
71. Malick A, Grant JA. Antihistamines in the treatment of asthma. *Allergy* 1997;52:52-63.
72. Advenier C, Queille-Roussel C. Rational use of antihistamines in allergic dermatological conditions. *Drugs* 1989;38:634-44.
73. Berth-Jones J, Graham-Brown RAC. Failure of terfenadine in relieving the pruritus of atopic dermatitis. *Br J Dermatol* 1989;121:635-7.
74. Marone G, Giugliano R, Lembo G, Ayala F. Human basophil releasability. II. Changes in basophil releasability in patients with atopic dermatitis. *J Invest Dermatol* 1986;87:19-23.
75. Greenberger PA, Patterson R, Radin RC. Two pre-treatment regimens for high-risk patients receiving radiographic contrast media. *J Allergy Clin Immunol* 1984;74:540-3.
76. Lasser EC, Berry CC, Talner LB, Santini LC, Lang EK, Gerber FH, et al. Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. *N Engl J Med* 1987;317:845-9.
77. Simons FER, Kesselman MS, Giddins NG, Pelech AN, Simons KJ. Astemizole-induced torsade de pointes. *Lancet* 1988;II:624.
78. Pratt CM, Hertz RP, Ellis BE, Crowell SP, Louv W, Moyé L. Risk of developing life-threatening ventricular arrhythmia associated with terfenadine in comparison with over-the-counter antihistamines, ibuprofen and clemastine. *Am J Cardiol* 1994;73:346-52.
79. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. *JAMA* 1993;269:1532-6.
80. Vigorito C, Poto S, Picotti GB, Triggiani M, Marone G. Effect of activation of the H₁ receptor on coronary hemodynamics in man. *Circulation* 1986;73:1175-82.
81. Vigorito C, Marone G, Condorelli M. Cardiovascular effects of histamine and sulfidopeptide leukotrienes. In: *Human Inflammatory Disease. Clinical Immunology*. Vol. 1 (Eds. Marone G, Lichtenstein LM, Condorelli M, Fauci AS). B.C. Decker Inc., Toronto, 1988; p. 107-23.
82. Marone G, de Crescenzo G, Adt M, Patella V, Arbustini E, Genovese A. Immunological characterization and functional importance of human heart mast cells. *Immunopharmacology* 1995;31:1-18.
83. Bhatti JZ, Hindmarch I. The effects of terfenadine with and without alcohol on an aspect of car driving performance. *Clin Exp Allergy* 1989;19:609-11.
84. Bradley CM, Nicholson AN. Studies on the central effects of the H₁-antagonist, loratadine. *Eur J Clin Pharmacol* 1987;32:419-421.
85. Genovese A, Spadaro G. Highlights in cardiovascular effects of histamine and H₁-receptor antagonists. *Allergy* 1997;52:65-76.
86. Vigorito C, Giordano A, De Caprio L, Vitale DF, Maurea N, Silvestri P, et al. Effects of histamine on coronary hemodynamics in man: role of H₁ and H₂ receptors. *J Am Coll Cardiol* 1987;10:1207.
87. Patella V, de Crescenzo G, Lamparter-Schummert B, Adt M, De Rosa G, Marone G. Increased cardiac mast cell density and mediator release in patients with dilated cardiomyopathy. *Inflamm Res* 1997;46 (suppl. 1):S3-S4.
88. Sale ME, Barbey JT, Woosley RL, Edwards D, Yeh J, Thakker K, et al. The electrocardiographic effects of cetirizine in normal subjects. *Clin Pharmacol Ther* 1994;56:295-301.
89. Meininger CJ. Mast cells and tumor-associated angiogenesis. In: *Human Basophils and Mast Cells: Clinical Aspects*. Vol 62 (Ed: Marone G). Basel, Karger, 1995; pp. 239-57.
90. Frase RA, Simpson JG. Role of mast cells in experimental tumour angiogenesis. In: *Development of the Vascular System*. (Eds. Nugent J, O'Connor M). Ciba Foundation Symposium 100. London, Pitman, 1983; pp. 120-31.
91. Zauberman H, Michaelson IC, Bergmann F, Maurice DM. Stimulation of neovascularization of the cornea by biogenic amines. *Exp Eye Res* 1969;8:77-83.
92. Roche WR. The nature and significance of tumour-assisted mast cells. *J Pathol* 1986;148:175-82.
93. Marks RM, Roche WR, Czerniecki M, Penny R, Nelson DS. Mast cell granules cause proliferation of human microvascular endothelial cells. *Lab Invest* 1986;55:289-94.
94. Schatz M, Hoffman CP, Zeiger RS, Falkoff R, Macy E, Mellon M. The course and management of asthma and allergic diseases during pregnancy. In: *Allergy: Principles and Practice* (4th ed). Vol 2 (Eds: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW). St. Louis, Mosby-Year Book, 1993; pp. 1301-42.