II. LITERATURE REVIEWS

A. MAST CELL DEVELOPMENT

I. In Animal Studies

Mast cells were discovered in1863 by F. Von Recklinghamsen and were named by Paul Ehrlich in the late 1870s (Ehrlich, 1877). He named them mastzellen (from the German "mastig" means well fed) after their granulation phenotype. The origin of these cells, however, remained obscure for many years ago. In fact, at one time or another, mast cells have been suggested to arise from T lymphocytes, macrophages, or fibroblasts (Burnet, 1977, Czarnetzki et al., 1982). It is now accepted that mast cells arise from pluripotential hematopoietic cells in the bone marrow. This was demonstratd by Kitamura and co-workers (Kitamura et al., 1978, Kitamura et al., 1981, Sonoda et al., 1989) with in vivo experiments using genetically mast cell-deficient mutant mice. The mutant, $WBB6_{F1}$-W/W^v mouse, ordinary is devoid of mast cells, but develops mast cells if it receives bone marrow cells either from its normal litermates ($WBB6_{F1}$-+/+ mice) or from semisyngenerated C57BL/6-bg/bg ("beige") mice. This approach revealed that mouse mast cells develop from bone marrow precursors.

II. In Human

It has been long proved difficult to culture human mast cells from blood or bone marrow in sufficient numbers to mast cell growth and differentiation. More recent work has defined the human mast cell progenitor population present in umbilical cord blood as $CD34^+$, $CD38^+$, HLA-DR (Kirshenbaum et al., 1991; Kempuraj et al., 1999).

Circulating progenitor mast cells are recognized by the surface expression of the receptor tyrosine kinase *c-kit* (CD 117), the receptor for SCF, a marker lost during the development of other hematopoietic cells including basophils (Valent and Bettelheim, 1992). Circulating progenitor mast cells express the receptor that binds immunoglobulin (Ig) G with low affinity, FcγRIIb, before the expression of the high-affinity receptor for IgE (FcεRI), and contain mRNA for mast cell proteases but lack

the distinctive metachromatic granules characteristic of mature mast cells (Rottem et al., 1994). Immature progenitor cells acquire the surface expression of FcεRI when exposed to both IL-4 and IgE (Toru et al., 1996, Yamaguchi et al., 1997). The differentiation of these mast cell progenitors requires the presence of SCF in all cases.

B. DISTRIBUTION AND IDENTIFICATION OF MAST CELLS

Mast cells are ordinarily distributed throughout normal tissues, where they often lie adjacent to blood and lymphatic vessels, near or within nerves, and beneath epithelial surfaces that are exposed to the external environment. Such sites include the dermis, the intestinal mucosa and submucosa, the conjunctiva, and the pulmonary alveoli and airways. The number of mast cells increases at inflammatory sites in atopic diseases, psoriasis, rheumatoid synovitis, and inflammatory bowel diseases. The numbers of mast cells in normal tissues exhibit considerable variation by anatomic site. Dermal mast cells are often located in close proximity to blood vessels, nerves, and lymphatics with an estimated density of 7,000 to 20,000 mast cells per cubic millimeter of skin (Damsgaard et al., 1997). However, unlike mature basophils, mature mast cells do not ordinarily circulate in the blood.

Mast cells can be identified by numerous granules that undergo red-purple metachromatic staining with the basic dye Toluidine blue. These cells exhibit a variable morphology, ranging from round to spindle-shaped with sizes up to 25 μm. A unilobed nucleus may be round to oval in shape and is typically eccentrically positioned. The cytoplasmic granules range from 0.3 to 0.8 μm in size and may occupy most of the cell volume. The cytoplasmic granules of human mast cells contain macromolecular complexes of proteoglycans and proteases that exhibit discrete patterns on electron microscopy (Weidner and Austen, 1990). Mast cells (MCs) express both tryptase and chymase (MC_{TC} or CTMC) demonstrate granules with a grating or lattice-like structure, whereas others contain only tryptase (MC_T or MMC) (lack detectable chymase less than 0.04 pg/cell) are with a scroll-like pattern. MMC predominate in lung and intestinal mucosa and CTMC predominate in skin, lung, and intestinal submucosa. Mast cells that apparently express chymase (MC_C) but no detectable tryptase have also been reported, but they represent only a minor population compared to MMC or CTMC.

C. MAST CELL ACTIVATION

I. FcεRI Dependent

Mast cell activation may be initiated upon interaction of a multivalent antigen (allergen) with its specific IgE antibody attached to the cell membrane via its high-affinity receptor, FcεRI. Cross-linkage of IgE by the interaction of allergen with specific determinants on the Fab portion of the molecule brings the receptors into juxtaposition and initiates mast cell activation and mediator generation and release. Experimentally, IgE cross-linkage may be induced artificially by the use of anti-IgE antibodies or antibodies against the IgE receptor. The subsequent crosslinkage of adjacent FcεRIs results in degranulation and transcription of inflammatory cytokines. During recent years it has become evident that not only IgE but also IgG can activate human mast cells to degranulate, by binding to the FcγRI (Woolhiser et al., 2001, Marone et al., 2002, Tkaczyk et al., 2002).

Mast cells can also be activated by neuropeptides, complement factors, C3a and C5a through C3aR and C5aR (CD88). Nerve growth factor can also activate mast cells through TRKA, and lectins by binding to the Fc region of FcεRI and thereby directly cross-linking it (Ansel et al., 1993, Nilsson et al., 1996, Nilsson et al., 1997). Morphologically, degranulation produced by immunologic and nonimmunologic stimuli appears similar. However, biochemical processes that lead to mediator release may differ.

II. Non-FcεRI Dependent

1. Basic compounds

A family of polybasic molecules is known to stimulate exocytosis from mast cells. Members of this family include compound 48/80, mastoparan, polymyxin B, and polymers of basic amino acids. These basic molecules appear to release histamine by interacting with the same site on mast cells, and in a noncytotoxic manner, leading to exocytosis and degranulation of mast cells (Matthews et al., 1989).

2. Peptides

A number of peptides have been shown to release histamine from mast cells. Several features of the secretions are shared by peptides and basic compounds such as

compound 48/80, including a rapid noncytolytic release, activation of signal transduction pathways, and selectivity regard to mast cell subtype. Histamine-releasing peptides may be divided into three groups; (1) peptides corresponding to the IgE C_H4 domain such as mellitin (the bee venom peptide), and adrenocorticosteroid hormone (ACTH), (2) neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), somatostatin, vasoactive intestinal polypeptide, and neurotensin, and (3) Rab3A peptide, is a small monomeric GTP-binding peptide and a member of the rab family of small G proteins.

3. Cytokines

A number of cytokines release histamine from mast cells. Interleukin-1, IL-3, and GM-CSF release histamine in the picomolar range, whereas platelet factor 4 and IL-8 release histamine at micromolar concentrations. Stem cell factor also degranulates mast cell in vitro and in vivo (Taylor et al., 1995). These factors have been referred to as inflammatory cell-derived histamine-releasing factors (HRFs). The chemokine macrophage inflammatory protein (MIP)-1α was reported to induce mast cell degranulation in vivo (Alam et al., 1994).

4. Anaphylatoxins

The complement fragments C3a, C4a, and C5a cause mast cell degranulation and elicits anaphylactoid reactions in vivo through specific receptors (Hugli and Muller-Eberhard, 1978, Gorski et al., 1979). Therefore, they are known as anaphylatoxins. C5a selectively activates human skin mast cells, with no effect on human lung mast cells (Schulman et al., 1988). The physiological relevance of anaphylatoxins has not yet been established, although they have been suggested as the mechanism by which histamine release is induced from mast cells in immune complex-mediated diseases.

D. MAST CELL-DERIVED MEDIATORS

Mast cells both release and generate a heterogeneous group of mediators that differ in their potency and biological activities. These mediators are both pleiotropic and redundant; that is, each mediator has more than one function, and mediators may overlap in their biological effects. For instance, histamine alters vasopermeability and induces mucus secretion, properties it shares with leukotriene C_4. Mast cell-

dependent mediators may be characterized into three groups; preformed secretory granule-associated mediators, lipid-derived mediators, and cytokines and chemokines.

I. Granule-Associated Mediators

1. Histamine

Histamine is a biogenic amine produced by mast cells, basophils, and platelets that is stored in secretory granules. Human skin mast cells contain approximately 1.9 μg of histamine per 10^6 cells (Schwartz et al., 1987). Secretory granule exocytosis and release of histamine occur rapidly in response to both immunologic and nonimmunologic stimulation (Lowman, 1988). Histamine acts through the H_1 receptor on target cells to cause increased venular permeability, flushing, bronchial and intestinal smooth muscle contraction, nasal mucus production, heart rate, and cardiac output. Actions mediated through the H_2 receptor include increased venular permeability, gastric acid secretion, and airway mucus production. Although an H_3 receptor has been identified, its function is unknown (Falus and Meretey, 1992).

2. Proteoglycans

The metachromatic staining of mast cell granules is due to sulfate, anionic proteoglycans composed of a novel peptide core, serglycin, common to all hematopoietic cell secretory granule proteoglycans, and of glycosaminoglycan adducts, including heparin, which is limited to mast cells (Avraham et al., 1989). Human mast cells stain metachromatically with toluidine blue and contain both heparin and chondroitin sulfate proteoglycans. Heparin may serve to stabilize histamine and proteases within the secretory granule and with granule exocytosis retains many of the proteases in a macromolecular complex (Goldstein et al., 1992). Proteases with a lysine- and arginine-rich binding face remain complexed in the exocytosed granule, whereas those with a histidine-rich binding face are released along with histamine at neutral pH (Ghildyal et al., 1996). Heparin is an anticoagulant, inhibits the complement cascade, and markedly potentiates the action of angiogenic factors. It may also inhibit the function of plasma membrane-associated low molecular weight group II and V PLA_2 through an association with critical lysine residues in a manner analogous to its interaction with proteases (Bingham et al., 1996, Murakami et al., 1996). Chondroitin sulfate E, like heparin,

has kinin pathway activation effects and proteases-stabilizing functions (Thompson et al., 1988).

3. Proteases

Tryptase is the predominant protease of the human mast cell (Irani et al., 1986). This serine-endopeptidase, as the name implies, exhibits trypsin-like substrate specificity by cleaving basic amino acid residues from proteins. Two human tryptase genes, α andβ, reside on chromosome 16 and are encoded by six exons (Miller et al., 1989). Both α- and β- tryptase are transcribed into pre-propeptides with a 30 amino acid leader sequence. The 31- to 34-kDa mature proteins are 92 percent homologous over 245 amino acids (Schwartz, 1995). The tryptase are cationic tetrameric proteins that form a macromolecular complex with heparin proteoglycan; these complexes are distinct from those containing chymase and carboxypeptidase, implying separate pathways of protease processing (Goldstein et al., 1992). Tryptase, a product nearly exclusive to mast cells, is a useful marker of in situ mast cell degranulation because its biologic half-life is longer than that of histamine (Schwartz et al., 1987). Human CTMC contain up to 5 μg of tryptase per 10^6 cells, with lesser amounts (10 μg per 10^6 cells) contained in those of the MMC phenotype (Schwartz et al., 1987). Low levels of tryptase, 0.4 percent that of mast cells, have been described in the basophil. Serum levels of tryptase rise within 15 min of anaphylactic events and peak at 1 to 2 h. Levels of tryptase elevated in mastocytosis due to an increased number of mast cells (Schwartz, 1995). Tryptase levels were increased in bronchoalveolar lavage fluids of patients with asthma or in nasal secretions from patients with allergic rhinitis reflect mast cell degranulation (Rasp and Hochstrasser, 1993).

Chymase is the chymotrypsin-like serine endopeptidase. The mature 30-kDa human mast cell chymase is encoded as a pre-propeptide with a 19 amino acid leader sequence, a 2 amino acid propeptide, and a 226 amino acid cationic mature enzyme that binds to heparin in a macromolecular complex. Adult human foreskin mast cells are estimated to contain 4.5 μg of chymase per 10^6 cells (Schwartz et al., 1987). Mast cell chymase has the following activities: a 100-fold greater potency than angiotensin-converting enzyme in the conversion of angiotensin I to angiotensin II; inactivation of bradykinin and the neuropeptides vasoactive intestinal peptide and substance P; cleavage of laminin, type IV collgen, and fibronectin with attendant basement

membrane degradation; direct activation of MMP-2 exceeding that of any other hematopoietic protease; conversion of the precursor of IL-1β to an active form; and stimulation of secretion from airway serous cells.

Carboxypeptidase A is not expressed in any other normal hematopoietic lineage has been localized in the CTMC subset of mast cells in intestinal submucosa and skin. The human carboxypeptidase A gene of 32 kb is located on chromosome 3 and is encoded by 11 exon. Carboxypeptidase A is encoded as a pre-propeptide with a 15 amino acid hydrophobic leader, a 94 amino acid activation sequence, and a 308 amino acid mature 34.5-kDa protein. Human foreskin mast cells are estimated to contain 16 μg of carboxypeptidase A per 10^6 cells. Carboxypeptidase A converts angiotensin I to angiotensin II and degrades neuropeptides. This endopeptidase, which is functionally similar to pancreatic carboxypeptidase B, functions at neutral to basic pH cleave carboxyl terminal aliphatic and aromatic amino acids from proteins after their expose to chymotryptic proteases.

II. Lipid-Derived Mediators

Membrane-derived phospholipids serve as the source of the 20-carbon arachidonic acid substrate that is utilized to form the eicosanoid products, prostaglandins (PGs) and leukotrienes (LTs), through intermediate enzymes. These lipid mediators are newly formed from membrane phospholipids after cell activation, in contrast to the preformed mediators that are stored within the secretory granule and released by exocytosis.

Prostaglandin D_2 is present in bronchial and nasal secretions after allergen challenge. Intradermal injection of PGD_2 leads to a wheal and flare response due to vasodilation and increased vasopermeability and inhalation of PGD_2 cause airway smooth muscle bronchoconstruction. PGD_2 inhibits platelet aggregation, is a neutrophil chemotaxin, and is an eosinophil activator.

Activated human mast cells produce the parent of the cysteinyl leukotrienes, LTC_4, along with far lesser amounts of LTB_4. LTC_4 increases microvascular permeability and is potent inducers of long-lasting wheal and flare responses. When inhaled, they elicit bronchoconstriction in normal individuals with more than 1000-fold greater potency than histamine. Levels of cysteinyl leukotrienes or their

metabolites are elevated in nasal secretions in patients with allergic rhinitis, in bronchoalveolar lavage fluid and urine from patients with asthma.

Platelet activating factor (PAF) is produced and secreted by stimulated mouse and human mast cells. PAF acts through a specific receptor as a chemotactic factor for eosinophils, neutrophils, monocytes, and macrophages. At a tissue level, PAF causes bronchoconstriction and vasopermeability, and is an important role in systemic anaphylaxis.

III. Cytokines and Chemokines

Human mast cells express a number of cytokines including TNF-α, IL-4, IL-5, IL-6, and IL-8 (Bradding et al., 1992, Okhawara et al., 1992, Bradding et al., 1993, Moller et al., 1993). Interleukin-4 is expressed preferentially by CTMC, whereas IL-5 and IL-6 were generally restricted to the MMC subset by immunostaining (Bradding and Holgate, 1999). There is also evidence that human mast cells produce chemokines. The human mast cell line HMC-1 is a source of multiple chemokines including I-309, MCP-1, MIP-1α, MIP-1β, and regulated on activation, normal T cell expressed and secreted (RANTES) (Selvan et al., 1994). Moreover, evidence has accumulated that human mast cells produce both IL-16 and the chemokine lymphotactin, both of which could contribute to the recruitment of lymphocytes at sites of mast cell degranulation (Rumsaeng et al., 1996, Rumsaeng et al., 1997).

E. MAST CELLS AND ALLERGIC INFLAMMATION

The immediate hypersensitivity reaction is the pathophysiologic hallmark of allergic rhinitis, allergic asthma and anaphylaxis, and the central role of the mast cell in the pathogenesis of these disorders is widely accepted.

In patients with atopic diseases, including allergic asthma, allergic rhinitis and atopic dermatitis, the sites of pathology contain complex inflammatory infiltrates including monocytes, macrophages, eosinophils, neutrophils, mast cells, basophlis and T cells, especially those that produce the Th2-type pattern of cytokines that can promote allergic responses. It is likely that all of these participants significantly influence the course of these allergic disorders and, in the aggregate, contributes to the local development of the pathology associated with these conditions.

F. ALLERGIC RHINITIS

Allergic rhinitis (AR), a chronic disease defined as a clinical hypersensitivity of the nasal mucosa to foreign substances mediated through IgE antibodies. AR usually develops symptoms in children before the age of 20 but also found in middle age and elderly. A family history of AR increases the odds of a child developing the disease. Atopy, the predisposition to respond to environmental allergens with the production of specific IgE antibodies, occurs in only 13% of children when neither parent is atopic, in contrast to 29% if one parent or sibling is atopic and 47% when both parents are atopic. A history of asthma is also likely (up to 4-6 times) to develop AR than are those in the general population. The role of the environment is also important since allergens, which are ubiquitous in virtually all environments, initiate and then, on subsequent exposure, trigger the genetically predetermined immune response. House dust mite and bacteria have been reported to associate in the pathogenesis of other atopic disorders, including broncial asthma and atopic dermatitis (Falanga et al., 1986; Shirakawa et al., 1997). Indoor allergens such as house dust mites, animal dander, cockroaches, and fungi are sensitized allergens for development symptoms of asthma. Bacteria could play a role in the pathogenesis of allergic inflammatory diseases. The colonization of *S. aureus* on atopic dermatitis lesions has been shown to correlate with cutaneous inflammation (Williams et al., 1990; Bunikowski et al., 2000). Bacterial superantigens and cell wall components has been reported to associate with the severity of the disease (Bachert et al., 2002; Matsui and Nishikawa, 2003; Rossi and Monasterolo, 2004).

I. Pathophysiology

After antigen is deposited on the nasal mucosa, it is engulfed by antigen-presenting cells (APCs; macrophages, dendritic cells, Langerhans cells, B cells and possibly epithelial cells) and is partially degraded within their phagolysosome. The antigens are proteolytically cleaved into 7-to-14 amino acid long peptides that bind to the antigen recognition sites of some major histocompatibility complex (MHC) class II (HLA-DR, DP, DQ) molecules. The types of polymorphic MHC class II molecules expressed by each person and the affinity of the molecules for specific antigenic peptides contributes to the “decision” of the immune system to develop or not to

develop an immune response to a specific protein (Schou, 1995). These APCs may traffic to adenoids and tonsils in the ring of Waldeyer and local draining lymp nodes. Antigen is presented to naïve Th0 lymphocytes that have been newly released from the thymus. It is presumed that these Th0 cells express cell-surface markers that allow them to home to airway mucosal vessels. In persons with an atopic diathesis, the antigen-specific T-cell receptors to Th0 cells recognize the antigenic peptides presented by MHC class II loci on APCs. Simultaneous contact is made between CD4 and MHC class II loci, CD28 and B7, and between other intercellular receptors and ligands on the T cell and APC, respectively. These composite factors trigger the peptide-specific Th0 cell to differentiate into Th2 lymphocyte. Newly minted Th2 cells become committed to release their characteristic combination of cytokines (IL-3, IL-4, IL-5, IL-9, IL-10, IL-13, GM-CSF, and possibly others), which may maintain the local pro-atopy environment, stimulate induction of B cell IgE production (IL-3, IL-4), and inhibit competing immune responses such as the development of Th1 delayed type hypersensitivity responses (IL-13, IL-4).

Newly generated IgM-bearing B cells that recognize sensitized allergen and receive appropriate CD40-CD40 ligand signals plus cytokines, such as IL-4, IL-6, IL-10, and IL-13, undergo heavy chain switching to produce IgE. B cell IgE production may be enhanced by exposure to aromatic hydrocarbons from diesel exhaust (Takenaka et al., 1995). Diesel exhaust particles also increase production of IL-2, IL-4, IL-5, IL-6, IL-10, and IL-13 mRNA and IL-4 protein from cells recovered in nasal lavage fluid (Diaz-Sanchez et al., 1996).

Circulating IgE binds to high-affinity Fcε receptors (FcεRI) on the surfaces of mast cells and basophils. Mast cells play an important role during the initial AR response. They exit in postcapillary venules in the mucosa and reside in the submucosal regions. During allergen assault, there is an increase in the proportion of epithelial mast cells (MMC) (Juluisson et al., 1995). Mucosal cells proliferate in allergic rhinitis, perhaps under the influence of Th2 cytokines (Kawabori et al., 1995). The allergen triggers mast cell degranulation that is the critical initiating event of acute allergic symptoms. Histamine, proteases, and other preformed mediators are released within seconds to a few minutes after mast cell activation. Here by they influence the early phase of an acute inflammation. Allergen-crosslinking of IgE on

the surface of the mast cell also activates tyrosine kinases, leads to activation of phospholipase A2, which release arachidonic acid from membrane phospholipids. Arachidonic acid can metabolized to be PGD_2 and LTD_4. They also act as important players in the acute phase of inflammation, and secretion starts a few minutes after activation and the production can continue for 30 minutes or more. Some of mediators produce the characteristic early symptoms of AR, namely sneezing, pruritus, rhinorrhea, and, to some extent, congestion whereas others will stimulate infiltration of the nasal mucosa with inflammatory cells, including basophils, eosinophils, neutrophils, newly sensitized mast cells, and mononuclear cells.

After 4-12 hours de novo synthesis and secretion of cytokines, chemokines, and growth factors start and reach the peak between 24-48 hours after activation. At this stage the late phase of the inflammation has begun, and the secreted cytokines and chemokines from mast cells recruit and activate other leukocytes. A variety of mediators are released by these cells, including leukotriene and histamine, all of which may be involved in the continued symptomatology and development of late phase inflammation.

II. Type of Allergic Rhinitis

The pathophysiologic process leads to the development of the AR symptoms: pruritus (itching), sneezing, congestion, runny nose/sniffing, and postnasal drip/snorting. These symptoms can quantify by a scoring system that measure of the severity of patients (Meltzer, 1988). Allergic rhinitis has always been subdivided based on the time of occurrence during the year, into seasonal and perennial disease. The recent Allergic Rhinitis and Its Impact on Asthma (ARIA) workshop proposes to replace these terms by intermittent and persistent rhinitis (Demoly et al., 2003). Intermittent or seasonal allergic rhinitis (SAR) has been appeared symptoms on the less than 4 days a week or for less than 28 days at a time. Persistent or perennial allergic rhinitis (PAR) has been appeared symptoms on the majority of days of the week and for more than 28 days. SAR is related to wide variety outdoor allergens such as ragweed, grasses, pollens, and outdoor moulds. PAR is most frequently caused by indoor allergens such as indoor moulds, cockroaches, and animal dander.

However, seasonal allergens in one region or country can be perennial allergens in another country and vice versa.

III. Evaluation and Diagnosis

1. History

The diagnosis of AR is highly dependent on a comprehensive history. Children may be able to provide accurate information in this regard if skillfully questioned and more information need to provide by parents or other caretakers. Signs and symptoms may be find and clinician may ask about the presence of allergens in the home and environment. The duration of patient's symptoms can be classified as SAR or PAR. Moreover, family history about atopic diseases may be questioned.

2. Physical examination

A complete ear, nose, and throat examination is essential in the work up of every patient suspected of having AR and is useful in identifying other problems rather than in confirming the diagnosis. The ear exam may show otitis media with effusion, suggesting nasophayngeal problems. Examination of the face may show puffiness of the eyelids and periorbital cyanosis, usually caused by venous stasis secondary to chronic nasal obstruction. Localized facial tenderness on palpation, especially in conjunction with purulent anterior or posterior nasal discharge, suggests sinusitis. External nasal examination may show a gross deformity due to previous trauma or bony expansion by an underlying lesion. A nasal speculum or an otoscope is then used to inspect the inner aspect of the nasal cavities for finding another complication and evaluation.

3. Diagnostic tests

The two most common tests used to confirm the diagnosis of AR are skin testing and in vitro testing for serum levels of specific IgE antibodies. Skin testing is performed by applying antigen extracts to the skin either epicutaneously (puncture skin tests) or intradermally (intradermal skin test). Testing is always accompanied by an injection of the diluent for the allergen extract, used as negative control, and histamine or codeine (a mast cell degranulating agent), used as a positive control. A wheal- and –flare reaction, seen within 15 minutes of injection, occurs if a patient is sensitive to a specific antigen.

Both total and specific serum IgE levels can be measured in vitro. Total IgE levels are elevated in 30-40% of patients with AR, and can be elevated in patients with nonallergic conditions and normal subjects, thus, total IgE determination is of limited use in the diagnosis of AR. The detection of specific IgE antibodies in the patient's serum by radioallergosorbent test (RAST) or other tests such as ELISA is useful in the diagnosis of AR. These tests eliminate the need for multiple skins pricks but are more expensive, and the results take longer to obtain than skin testing.

Radiologic tests can be useful in identifying other causes of nasal obstruction and chronic sinusitis. Lateral films of the head and neck facilitate the diagnosis of adenoid hypertrophy in a child; computerized axial tomography of the midface can be used to identify or rule out unilateral or bilateral choanal atresia or stenosis, coronal sinus. CT scans can be used to evaluate the sinuses. These tools are used if AR does not explain the clinical symptoms, when other entities are suspected, or when the patient does not respond appropriately to treatment.

Nasal cytology has been utilized as a diagnostic tool for differentiation of AR in children and adults (Lee et al., 1993, Jirapongsananuruk and Vichyanond, 1998). Nasal cytological studies can aid in classifying the rhinitis of individual patients into inflammatory, non-inflammatory, and structurally induced categories. It also differentiates between allergic, nonallergic, and infectious forms of rhinitis and between bacterial and viral infection. Analysis of the nasal cell specimen can classify cellular immune responses of eosinophils, basophils, neutrophils, and globlet cells. In allergic rhinitis, nasal cytology showed inflammatory cell infiltration that involved in increasing nasal symptoms. BMC and eosinophils in the nasal epithelium increased in number and thought to play an important role in nasal allergic manifestation. Moreover, this method also used to follow up and evaluate patient's compliance.

Combining the information obtained from the history, physical examination and diagnostic tests can be used to confirm the diagnosis of AR.

IV. Management of Allergic Rhinitis

1. Avoidance

Allergen exposure leads to symptoms. Thus allergen avoidance is the most effective treatment for AR. Outdoor allergens such as grasses, trees, or ragweed are

difficult to control, and patients should be instructed to avoid activities that increase exposure. For indoor control, keeping windows closed and installing an electrostatic filter on central air conditioning can be helpful. Unfortunately, it is also often highly impractical; individuals frequently are sensitized to multiple allergens, making it difficult. As a result, pharmacotherapy is required frequently.

2. Pharmacotherapy

Antihistamines are the oldest drugs used in the treatment of allergic disorders. First-generation antihistamines have significant sedative and anticholinergic effects resulting from their ability to cross the blood brain barrier, and they should be avoided for the treatment of AR. Second-generation antihistamines have a longer duration of action and minimal, if any, sedative effects. These drugs reduce pruritus, sneezing, and watery rhinorrhea associated with AR but have minimal effects on nasal obstruction. Antihistamines are uniquely effective for acute allergic reactions, which are mediated predominantly by mast cell-derived histamine, and might be beneficial in patients with intermittent allergen exposures, such as occasional outdoor exposure during the pollen season.

Decongestants produce vasoconstriction within the nasal mucosa through a-adrenergic receptor activation and are thus effective in relieving the symptoms of nasal obstruction. Topical decongestants can be either catecholamines or imidazoline derivatives, have a rapid onset of action, and are usually more efficacious than systemic decongestants but continued usage of these agents lead to progressively shorter duration of action. However, these agents have no effect on other symptoms, such as rhinorrhea, pruritus, or sneezing. Therefore, they may be most effective when used in combination with other agents, such as antihistamines.

Anticholinergic drugs are useful in the treatment of those subjects in whom rhinorrhea is the predominant complaint. This agent can also be used in conjunction with other therapeutic modalities such as antihistamines or intranasal steroids for the satisfactory control of rhinorrhea.

Leukotriene modifiers are effect on inhibition of the 5-lipoxygenase pathway and leukotriene receptor antagonists. However, leukotriene modifiers might be acting secondarily to reduce inflammation in the airway, including production, recruitment, and activation of histamine-producing cells, such as mast cells and basophils.

Mast cell stabilizers, such as cromolyn sodium, can be useful in relieving nasal pruritus, rhinorrhea, sneezing, and obstruction; however, they have minimal effect on congestion. Cromolyn sodium is generally well tolerated and is most efficacious when taken prophylactically, well in advance of allergen exposure. When effective, the potency of this agent parallels that of antihistamines but is less than that of intranasal steroids.

Glucocorticosteroids are among the most poten t treatments available for AR. The role of systemic steroids in the treatment of AR is limited because of their adverse effects and the limited morbidity of the disease. Intranasal corticosteroids are considered first-line therapy in the management of adults with moderate-to-severe SAR or PAR (Bousquet et al., 2001). These effects include decrease in numbers of epithelial Langerhans cells, mast cells, IL-4 immunoreactive cells, Th2 cells (Holm et al., 1995), and epithelial and submucosa eosinophils by increasing eosinophils apoptosis (Baraniuk, 1996). Regular prophylactic use of intranasal corticosteroids effectively reduces sneezing, pruritus, watery rhinorrhea, and nasal blockage in both children and adults. Since oral decongestants, with intranasal steroid preparations cannot be delivered because of nasal obstruction, a short course of systemic steroids is effective in relieving nasal obstruction.

3. Immunotherapy

Immunotherapy is usually reserved for patients who find it difficult to avoid allergens and who have not responded adequately to pharmacologic treatment. The treatment offers relief, but the onset of action is slow, with improvement starting within 12 weeks and increasing over a period of 1-2 years after treatment. Immunotherapy involves the repeated administration of increasing doses of allergen extract in an attempt to alter patient's immunologic responses and improve their symptoms. Since its introduction in 1911, many studies have supported its effectiveness in the treatment of pollen allergies. Several immunologic changes occur in patient's receiving immunotherapy and these include:

(1) A rise in serum-specific IgG

(2) An increase in the level of IgG and IgA antibodies in nasal secretion

(3) A variable reduction in the reactivity and sensitivity of peripheral mast cells and basophils to allergens

(4) Reduced in vitro lymphocyte responsiveness to allergens

(5) A reduction in inflammatory cells in the nasal mucosa and nasal secretions, accompanied by a shift from the Th2 to Th1 cytokine profile

(6) Suppression of the seasonal rise in IgE antibodies followed by a slow decline in the level of specific antibodies during the following several years of treatment.

It is important to identify carefully all allergens responsible for the patient's symptoms before initiating treatment because the treatment involves multiple visits, requires a high degree of patient compliance, is highly specific and effective only for the allergen administered, and need months to achieve clinical improvement.

G. HOUSE DUST MITES

House dust mite is classified the phylum Arthropoda, belong to the suborder Astigmata and family Pyroglyphidae. However, mites belonging to other families are also present in house dust, and the term domestic mites include both mites from the Pyroglyphidae family or dust mites and mites from other families. Thirteen species have been found in house dust, 3 of which are very common in homes worldwide and are the major source of mite allergen. The most common of these species are *Dermatophagoides farinae* (Df), *Dermatophagoides pteronyssinus* (Dp) and *Euroglyphus maynei* (Em), which are found in temperate climates. In tropical climates, the storage mite *Blomia tropicalis* (family Echymyopodidae) can be prevalent mite in dwellings, along with other Pyroglyphid mites (Arlian, 2001). House dust mites have been known to be associated with allergies since the 1960's. They are so tiny that are virtually invisible without magnification. They pass through six developmental stages including egg, active larva, resting larva (pharate tritonymph), active tritonymph, resting tritonymph (pharate adult), and active adult. Between 19 to 30 days are needed to complete a life cycle depending upon the temperature and humidity. They survive best at relative humidities of 70-80 % and temperatures of 75-80 ° F. Mated females live about two months. A male may attach itself to a tritonymph female and mate when she reaches the adult stage. Adult female mites lay cream-colored elliptical eggs three times a day. They concentrate at high traffic area in homes and on certain furniture items, especially beds, upholstered

lounges, chairs, and in carpets with long fibers. They feed on shed skin of man. The average individual sheds 0.5 to 1.0 gram of skin daily. They do not bite or sting but harbor strong allergens in their bodies as well as in their secretions, excreta and shed skins. Mite allergens mainly present in feces and mites produce over 20 fecal pellets or guanine per day that over 200 times it's own body weight during it lifetime. The powerful enzymes in mite droppings are the main cause of allergy in sensitive people.

Group 1 allergens of the mites Der p1 and Der f 1 are the most significant allergens; 80 % to 95 % of patient's allergic asthma to dust mites has an elevated IgE response to them (Platts-Mills et al., 1992). Purification of Der f1 and Der p1 allergens has been achieved by a combination of 50 % saturated ammonium sulphate precipitation and gel filtration or by affinity chromatography with specific monoclonal antibodies (Heyman et al., 1986, Vander Zee et al., 1988). In most clinical studies, due to the difficulty of obtaining large amounts of purified group 1 allergens, dust mite-specific IgE has been measured by RAST, ELISA, or Pharmacia CAP system using crude mite extracts. The conventional technique used in these assays is to immobilize mite allergens on a solid medium such as paper disks (RAST) or polystyrene microtiter plates (ELISA), or hydrophilic polymers (CAP).

Identification of dust mites is performed with the use of light microscopy and taxonomic keys, after the specimen has been extracted by flotation and/or sieving methods from the dust samples and especially prepared on a glass slide. Several strategies have been used in an attempt to control HDM, including killing mites by physical or chemical methods and encasing the bedding with an allergen-impermeable cover for blocking the leakage of dust mites and their fecal pellets from bedding, which is considered the first approach in allergen avoidance. Specific allergen immunotherapy (desensitization or hyposensitization) is the technique of treating IgE-mediated diseases with increasing doses of an allergen in order to decrease sensitivity to that allergen. Recently, culture and harvesting of pure mite bodies is performed to use as mite antigen or extracts for diagnostic and treatment.