MAST CELLS AND MASTOCYTOSIS:
Developments Over The Last Decade

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INTRODUCTION

Mastocytosis is an uncommon clinical disorder that is characterized by an increased number of tissue mast cells. While the cutaneous manifestations of this disorder have been recognized for over a century it has been only over the last decade, with our increased awareness of the importance of the mast cell in health and disease, that interest in this disorder has heightened.

The effector role of mast cells in allergic diseases is well-recognized. In addition, however, it is now known that these cells participate in a variety of processes, both physiologic and pathophysiologic. While most considerations of mast cell function have focussed on the pathologic role of the inflammatory mediators contained within the mast cell granules, the recent demonstration of the production, upon activation, of cytokines and growth factors suggests a role for mast cells in the growth and development of a variety of cells. Also, the strategic location of mast cells - in the lymphoid tissues, around blood vessels and nerves, throughout connective tissues and in tissues that interface with the environment - adds further evidence that these cells fulfill a number of regulatory functions. Indeed, evidence exists to suggest that mast cells not only provide a critical defense against certain parasites, but in addition, they also have been shown to play a role in the regulation of lymphoid responses, stimulation of connective tissue repair and maintenance of the vasculature. While much of our knowledge over the last decade has stemmed from work done in animals, studies of patients with mastocytosis has allowed us to gain enormous insight into the biologic properties and functions of the mast cell and mast cell disease.

HISTORICAL PERSPECTIVE

Nettleship and Tay (1) are credited with the first description of mastocytosis. In 1869 they reported a two year old girl with persistent, hyperpigmented lesions that spontaneously urticated. It was not until 1877, however, that mast cells actually were described. Upon staining connective tissue with aniline dyes, Paul Ehrlich (2) found that certain cells possessing cytoplasmic granules stained metachromatically. He chose the term *mastzellen*, derived from the German word "to chew", to describe these cells since he believed the presence of the granules resulted from overfeeding. In addition to being credited with their initial description, Ehrlich also described the process of degranulation and noted the association of mast cells with blood vessels, inflamed tissues, nerves and neoplastic tissue. Subsequently, in 1878 Sangster (3) described a patient with a pruritic, pigmented urticarial rash and he labeled this cutaneous eruption urticaria pigmentosa. The importance of mast cells in this disorder was not discovered, however, until 1887 when Unna and Beitrage (4) demonstrated the presence of large numbers of dermal mast cells in the skin lesions of affected patients. It was not until 1936, almost 50 years later, that Sezary and colleagues (5) coined the term "mastocytosis". Subsequently, Ellis (6) who formally showed that other organs, including the liver, spleen, thymus, bone marrow, pancreas and lymph nodes may be affected by this disease process.

THE MAST CELL

Morphology and Distribution

Mature human mast cells may be round, spindle-shaped or spiderlike and are usually 9 to 12 μm in diameter. The plasma membrane contains elongated folds and may appear ruffled by transmission electron microscopy. Unlike the lobulated nucleus of the basophil, the mast cell nucleus is round or oval and is elliptically situated in the cell. The most characteristic feature of the mast cell is the beautiful array of metachromatic granules. These may comprise a large amount of the dry weight of the cell (7) and as much as half its volume (8). Ultrastructurally, there are differences in granule morphology among species. While rodent mast cell granules have an amorphous appearance, human mast cell granules demonstrate a variety of patterns.

Mast cells are positioned in connective tissue and mucosal surfaces at potential sites of entry of noxious substances. The tissues in which they predominate include those that interface with the outside environment where allergic reactions most often occur and include the skin, gut, conjunctivae and respiratory tract. While bone and cartilage have few mast cell numbers, large numbers are found around blood vessels and in the alveolar wall, dermis and mucosa of the nose, bowel and conjunctivae.

Origin and Development

Only recently has the origin of mast cells been clearly delineated. Due to their connective tissue location there was a great deal of confusion regarding their derivation. After their discovery, a number of proposed cells of origin were suggested: T cells, fibroblasts, mesenchymal cells, plasma cells, histiocytes, endothelial cells, and degenerate cells (9-11, reviewed in 7). It was also thought that since mast cells and basophils both contain metachromatic granules, histamine, and high affinity IgE receptors, these two cells were intimately related in lineage. We now know that while these cells are similar in some respects, they can easily be distinguished by their nuclear morphology, mediator content, location and response to activating agents. Moreover, basophils are terminally-differentiated cells that, after maturation in the bone marrow, are released into the peripheral blood. In contrast, it is now clear that mast cells are released from the bone marrow as progenitors to complete their differentiation in the peripheral tissues.

The bone marrow origin of mast cells was first clearly demonstrated by Kitamura and colleagues (12,13) in a series of *in vivo* reconstitution experiments using genetically mast cell-deficient mutant mice and their genetically normal littermates. Mutations at the dominant white-spotting (*W*) locus on mouse chromosome 5, and the steel (*Sl*) locus on chromosome 10 affect several critical developmental processes including gametogenesis, pigmentation, and hematopoiesis. In addition, Kitamura et al. (12,13) demonstrated that mutations at either of these loci also dramatically affected mast cell

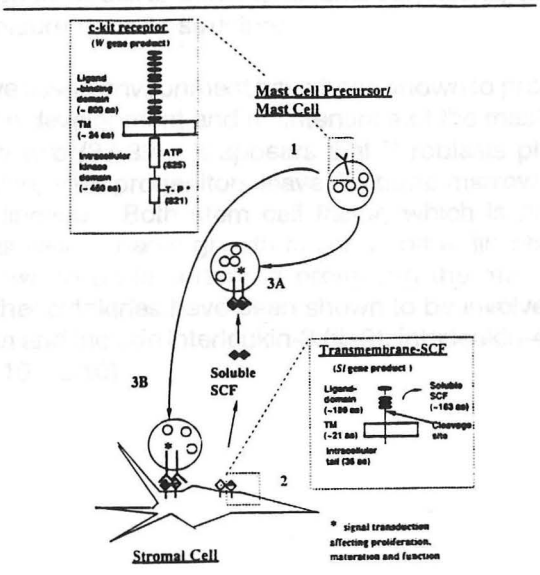
development. They found that transplantation of congenic +/+ bone marrow cells corrected the mast cell defect of *W/W^v* mice but not *Sl/Sl^d* mice (12). The mast cell defect of *W/W^v* mice was also corrected by transplanted bone marrow from *Sl/Sl^d* mice (13). Taken together, these findings demonstrate that the *W/W^v* mutants have a deficiency within the mast cell precursor population, whereas the *Sl/Sl^d* mutants have normal bone marrow progenitors for mast cells but a defective microenvironment which is necessary for normal mast cell differentiation.

The explanation on a molecular level for these mast cell deficiencies has been provided within the last few years when the gene products of the *W* and the *Sl* loci were cloned (14-20). It was demonstrated that the c-*kit* proto-oncogene, which encodes c-*kit*, a tyrosine kinase receptor expressed on mast cells, maps to the *W* region. Identification of the c-*kit* receptor as the *W* gene product subsequently set the stage for the elucidation of its ligand. Within a short time, three groups reported simultaneously the cloning and characterization of a new hematopoietic growth factor that represented the product of the *Sl* locus and a ligand for the c-*kit* receptor (17,18,20-24). This factor which has been termed stem cell factor (SCF) (23), kit ligand (KL) (25), mast cell growth factor (MGF) (21), and Steel factor (26) is highly expressed on fibroblasts and stromal cells and has been found to play a major role in mast cell proliferation and maturation.

Figure 1

c-kit *Receptor/c-kit* Receptor Ligand (SCF) Interactions in Mast Cell Development

(1) Both mast cell precursors and cells in the mast cell lineage express the c-kit receptor on their surface. The structure of the receptor includes a transmembrane portion (TM), an ATP binding site, and the tyrosine autophosphorylation (T-P*) site. (2) A stromal cell expresses transmembrane SCF, including the cleavage site for generation of soluble SCF. (3) Interaction of the mast cell precursor or mast cell with the soluble (A) or transmembrane (B) SCF induces signal transduction in the mast cell precursor/mast cell (Ref 27).



While *in vitro* studies have expanded our knowledge regarding the growth and differentiation of murine mast cells, similar studies of human mast cells have been hampered by the inability to culture sufficient mast cell numbers from human blood and bone marrow. Recently, however, small numbers of mast cells were cultured and examined using a technique whereby human bone marrow-derived mononuclear cells were suspended over agar (28) or agarose (29) in the presence of human recombinant interleukin-3 (rhIL-3). The cells produced stained histochemically like mast cells and possessed high affinity IgE receptors and contained the neutral protease tryptase within cytoplasmic granules, all characteristic features of human mast cells (30).

Despite the demonstration that human mast cells could arise from bone marrow-derived mononuclear cells, their derivation remained unclear. Reports were conflicting. While human skin, colon, and spleen mast cells were not found to possess T-cell, B-cell, or monocyte markers (21) they were found to possess surface markers associated with a late stage of monocyte/macrophage but not basophil differentiation (32). In experiments designed to remove committed T-cell (CD2), B-cell (CD19 and CD20), eosinophil and macrophage (CD14) precursors from human bone marrow, bone marrow-derived mononuclear cells continued to give rise to mast cells. However, when CD34+ pluripotent progenitor cells were removed from the culture mast cells did not arise. Additional experiments, using highly enriched CD34+ cells cultured in the presence of rhIL-3 over agarose, yielded mast cells in small numbers (33). The granules that were produced contained homogenous material, not the scroll or lattice patterns characteristic of mature mast cells. Taken together, these studies demonstrate that human mast cells originate from a pluripotent CD34+ progenitor cell and that additional conditions/factors are required for the development of mature granule structure.

Both fibroblasts and a connective tissue environment have been shown to provide the additional conditions needed for the development and maintenance of the mast cell phenotype both *in vitro* (34-36) and *in vivo* (37-39). It appears that fibroblasts play a critical role late in mast cell differentiation, after progenitors leave the bone marrow and become committed to the mast cell lineage. Both stem cell factor, which is highly expressed on the fibroblast surface, as well as nerve growth factor, another fibroblast-derived growth factor, have been shown to be important in promoting the mast cell phenotype. In addition, a variety of other cytokines have been shown to be involved in mast cell proliferation and differentiation and include interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-9 (IL-9) and interleukin-10 (IL-10).

Figure 2

MAST CELL PROLIFERATION AND DIFFERENTIATION

Confirmation of bone marrow origin:
CD34+ progenitor cell

Mast cell growth factors:

Interleukin-3
Interleukin-4
Interleukin-9
Interleukin-10
Nerve growth factor
Stem cell factor (c-*kit* Ligand)

Heterogeneity

Two major types of mast cells have been identified in both rodents and humans and, as stated in a recent review by Schwartz and Huff (40), "recognition of this complexity is crucial for understanding mast cell biology and, potentially, for treating mast cell-associated disease" (41). "Mucosal" and "connective tissue", the most common terms used to describe the two mast cell types, are phenotypic descriptions. Unlike rodent mast cells, human mast cell types can not be differentiated from each other by their histamine or heparin proteoglycan concentration. However, they can be distinguished by their neutral protease composition (42,43): MC_T contain tryptase alone and correspond to the mucosal mast cell phenotype (MMC) while MC_{TC} contain tryptase, chymase, carboxypeptidase and a cathepsin G-like enzyme and correspond to the connective tissue phenotype (CTMC).

In histologically normal tissues MC_T cells are found predominantly in the alveoli of the lung and in the intestinal mucosa, while MC_{TC} cells are found mainly in the skin and intestinal submucosa. Despite the fact that one particular mast cell type may predominate in a tissue, a mixture of these two cell types is usually seen. For this reason, MC_T and MC_{TC} cells can not be differentiated from each other based upon their location alone.

Ultrastructurally, these two cell types differ as well. Studies have shown that the secretory granules of the MC_T cells have variable shapes and are smaller than those of the MC_{TC} cells. The majority of the MC_T cells possess granules with discrete scroll-like structures whereas grating and lattice structures predominate in the MC_{TC} cells.

Figure 3

Characteristics of Human Mast Cell Types*

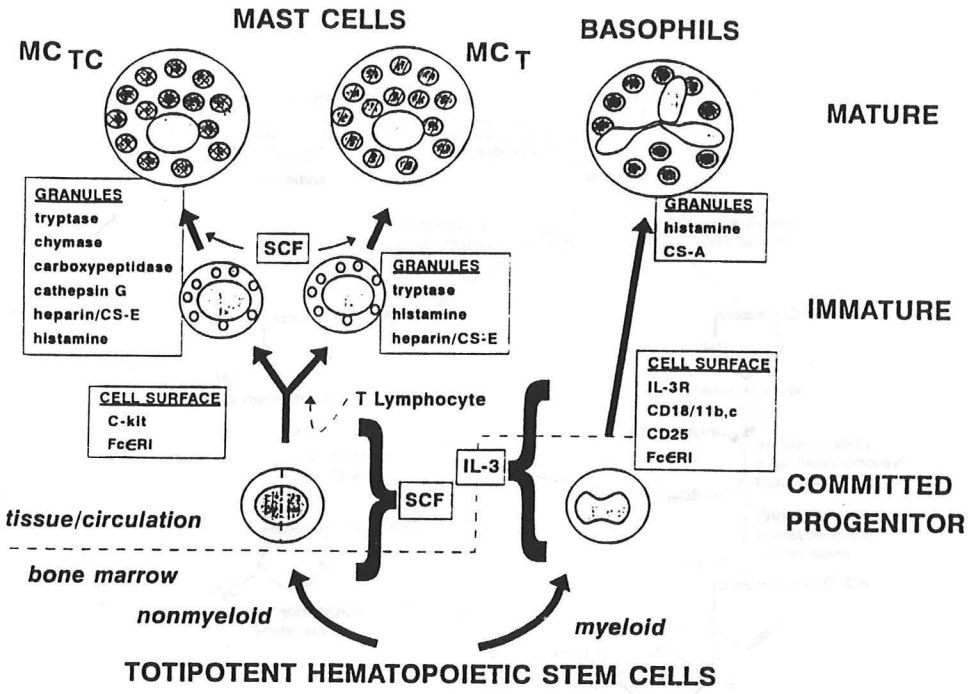
Characteristic	MC_{TC} Cell	MC_T Cell
Tissue Distribution		
Skin	++	-
Intestinal submucosa	++	+
Intestinal mucosa	+	++
Alveolar wall	-	++
Bronchi/bronchioles	+	++
Nasal mucosa	++	++
Conjunctiva	++	+
Synovium	++	-
Protease content	Tryptase, chymase cathepsin G-like protease, carboxypeptidase	Tryptase
T lymphocyte dependency	No	Yes
Granule morphology	Grating/lattice Complete scroll poor	Complete scroll rich

*Modified from Schwartz and Huff, Biology of Mast Cells and Basophils in *Allergy-Principles and Practice*, 1993.

The issue of whether or not two distinct mast cell lineages exist for human MC_T and MC_{TC} types is still unresolved. However, evidence exists to suggest that these cell types may develop along distinct pathways. Both humans with inherited combined immunodeficiency and those with the acquired immunodeficiency syndrome have marked decreases in their MC_T cell concentrations in the bowel, while the MC_{TC} cell numbers and distribution are unchanged (30). This finding suggests that MC_T cells develop along a pathway that is dependent upon the existence of functional T lymphocytes while MC_{TC} cell development is T lymphocyte-independent.

Figure 4

Developmental Pathways for Human Mast Cells and Basophils*



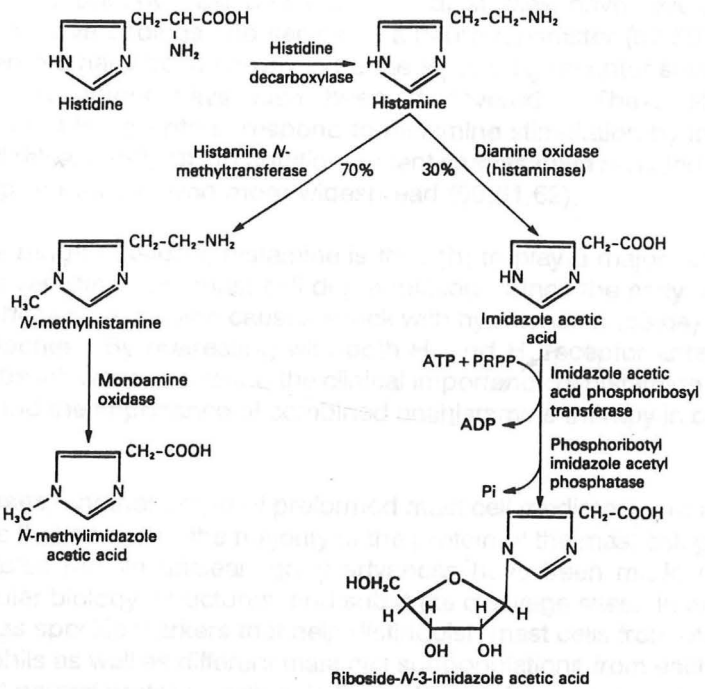
*From Schwartz and Huff, Biology of Mast Cells and Basophils in *Allergy-Priniciples and Practice*, 1993.

Preformed Mast Cell Mediators

Histamine, the sole, major biogenic amine in human mast cells, is formed from histidine (45) by histidine decarboxylase (46). It is present in concentrations of 4-10 pg/cell and is the only preformed mediator of human mast cells that has potent, direct vasoactive and spasmogenic effects. Histamine is released within 30-45 seconds after activation and produces its effects on the vasculature within 1-5 minutes (47). After it is released, histamine is metabolized by one of two pathways (48,49): methylation (70%) or oxidation (30%). Metabolism by diamine oxidase (histaminase) yields imidazole acetic acid, while metabolism by *N*-methyltransferase yields *N*-methylhistamine and *N*-methylimidazole acetic acid. The methylation products are excreted by the kidney and may be measured in the urine as a measure of endogenous histamine release. Metabolism occurs within minutes of release suggesting that histamine acts locally and not on distant target tissues.

Figure 5

HISTAMINE SYNTHESIS AND METABOLISM



The biologic effects of histamine are wide-ranging and are mediated through the activation of three receptor subtypes, termed H_1 and H_2 and H_3 receptors. These receptors are present on a variety of tissues and circulating cells, and their activation results in a variety of biologic responses. H_1 receptor activation results in airway and gastrointestinal smooth muscle contraction, increased capillary permeability and prostaglandin and thromboxane production. Activation of H_2 receptors also causes increased vasopermeability but, in addition, causes mucous production and gastric acid secretion. Other H_2-mediated effects include inhibition of: basophil histamine release (50), delayed hypersensitivity skin test responses (51) and *in vitro* generation of cytotoxic T lymphocytes (52). Stimulation of H_2 receptors on neutrophils and eosinophils results

in the inhibition of lysosomal enzyme release from neutrophils and modulation of migration of both cell types (53). H_2 receptor activation of lymphocytes has also been demonstrated to inhibit several B-cell responses including: antigen-stimulated B-cell maturation (54), secretion of antibody by plasma cells (53) and antibody production by human mononuclear cells (55). Activation of H_2 receptors on T lymphocytes leads to the production of cytokines (56).

Recently, both immunochemical and biochemical studies have revealed that histamine is present in nerve endings and serves as a neurotransmitter (57-59). While the postsynaptic receptors have been shown to be the H_1 and H_2 receptor subtypes, a class of presynaptic receptors have also been discovered. These inhibitory autoreceptors, designated H_3 receptors, respond to histamine stimulation by inhibiting both its synthesis and release (59,60). In addition, recent studies have revealed that the functions of this receptor may be even more widespread (59,61,62).

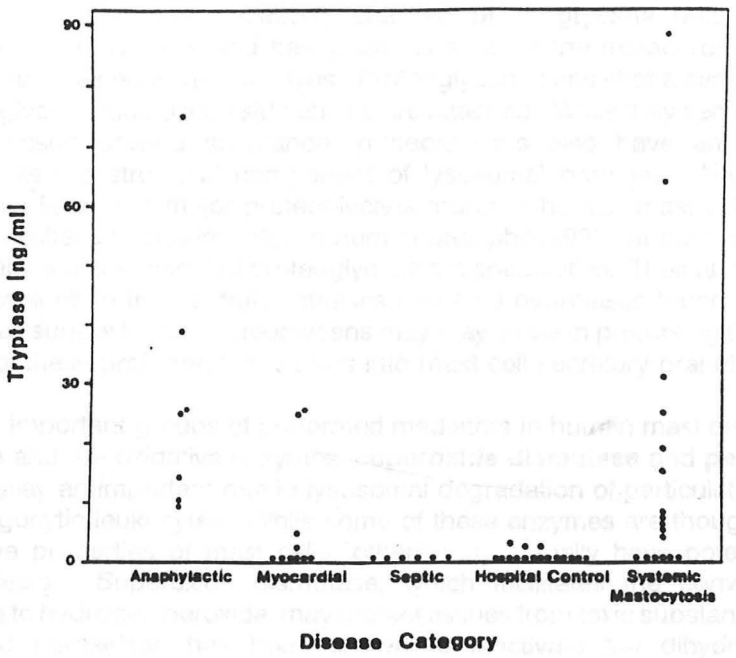
Due to its wide range of effects, histamine is thought to play a major role in the clinical manifestations resulting from mast cell degranulation. Since the early 1900's it has been known that histamine infusion causes shock with hypotension (63,64), as well as flushing and headaches. By pretreating with both H_1 and H_2 receptor antagonists these symptoms can be inhibited, indicating the clinical importance of histamine in mast cell mediated events and the importance of combined antihistamine therapy in blocking its systemic effects.

Neutral proteases, another group of preformed mast cell mediators, are a group of proteolytic enzymes that comprise the majority of the protein of the mast cell granule. While their biologic roles remain unclear, great advances have been made recently regarding their molecular biology, structures, and substrate cleavage sites. In addition, these enzymes serve as specific markers that help distinguish mast cells from other cell types including basophils as well as different mast cell subpopulations from each other. While the predominant neutral protease activity in the rodent is chymotryptic, the neutral proteases in humans have been found to be tryptic in nature.

Tryptase is the major enzyme accounting for the trypsinlike activity demonstrated by human mast cells (65,66). While the biologic role of tryptase has not yet been clearly demonstrated, it may be important in fibrinogenolysis and latent collagenase activation (67,68). Tryptase is found in both MC_{TC} and MC_T cells and is released along with histamine during the degranulation process (69). Negligible amounts of tryptase have been found in basophils while other cells possess none. Thus, this enzyme is a specific marker of human mast cells. Taking advantage of this important and useful finding, Schwartz and colleagues (70-75) recently developed a very sensitive and specific assay to measure tryptase in a variety of biological fluids. By demonstrating that this enzyme is elevated in patients with anaphylaxis and mastocytosis but not those with other systemic disorders, they documented its usefulness as a specific indicator of systemic mast cell activation (70).

Figure 6

LEVELS OF TRYPTASE IN HOSPITALIZED PATIENTS*



*From Schwartz et al., Tryptase Levels as an Indicator of Mast-Cell Activation in Systemic Anaphylaxis and Mastocytosis. N Engl J Med 316:1622, 1987 (Ref 70).

Chymase is the major enzyme that accounts for the chymotryptic activity in human cutaneous mast cells. This enzyme has been purified (76) and recently, the gene has been cloned (77). Unlike tryptase, chymase is found in a subpopulation of mast cells, the MC_{TC} subtype, localized to the gastrointestinal submucosa and the skin. Like tryptase, the biologic activities of chymase are not well-understood. Potential interesting findings include the ability of chymase to: efficiently convert angiotensin I to angiotensin II (78), inactivate bradykinin (79) and attack the lamina lucida of the basement membrane at the dermal-epidermal junction of human skin (80). It is thought that this latter function may account for the blister formation seen in infants with systemic mastocytosis.

The most recent neutral protease that has been cloned and characterized from human mast cells is carboxypeptidase (81-90). It, along with cathepsin G-like protease, is present in MC_{TC} cells and helps to extend the compositional differences between the two human mast cell subtypes.

The highly sulfated and negatively charged **proteoglycans** present in the secretory granules of mast cells and basophils account for the metachromasia seen when these cells are stained with basic dyes. Proteoglycans consist of a central protein core from which glycosaminoglycan side chains are attached. While they serve as major constituents of tissue ground substance, proteoglycans also have an important intracellular role as the structural component of lysosomal granules. Heparin and chondroitin sulfate E are the major proteoglycans found in human mast cells (91,92) while chondroitin sulfate A predominates in human basophils (93). At the present time the biologic functions of the mast cell proteoglycans are speculative. Their ability to bind to histamine as well as to the neutral proteases and acid hydrolases found within the secretory granules suggests that proteoglycans may play a role in promoting the uptake and packaging of these preformed mediators into mast cell secretory granules.

Two other important groups of preformed mediators in human mast cells are the **acid hydrolases** and the oxidative enzymes, **superoxide dismutase** and **peroxidase**. These enzymes play an important role in lysosomal degradation of particulate material ingested by phagocytic leukocytes. While some of these enzymes are thought to add to the destructive properties of mast cells, others may actually have potential anti-inflammatory effects. Superoxide dismutase, which facilitates the conversion of superoxide anion to hydrogen peroxide, may protect tissues from toxic substances, while mast-cell derived peroxidase has been shown to inactivate the dihydroxy- and sulfidopeptide leukotrienes (94).

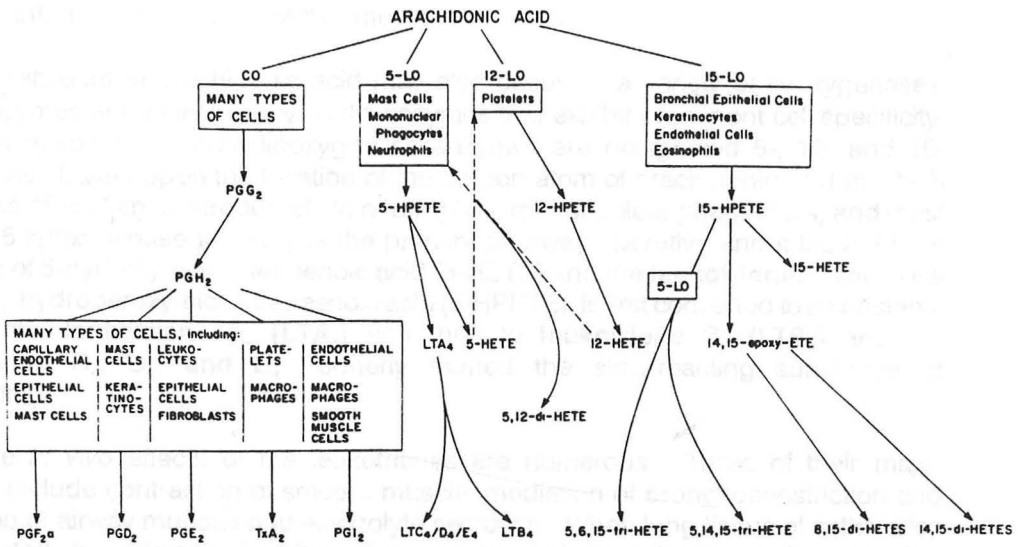
The final group of preformed mast cell mediators are the **chemotactic factors**. A neutrophilic chemotactic factor, thought to arise from mast cells, has been demonstrated in both patients with atopic asthma (95-97) after airway challenge with inhaled allergen and those with physical urticarias (98-100) after provocation of the skin. In addition, eosinophilic chemotactic factors have been demonstrated as well. When stimulated *in vitro* by antihuman IgE human lung tissue has been shown to release an eosinophil chemotactic factor (101). This factor was localized to the mast cell and was termed eosinophil chemotactic factor of anaphylaxis (ECF-A) (102). The potential clinical relevance of this finding is seen in patients with cutaneous mastocytosis where oftentimes the infiltrating cells in the skin include eosinophils (103).

Newly-Generated Mediators

Upon activation arachidonic acid is released from intracellular lipid stores. It may undergo oxidative metabolism via the cyclooxygenase pathway to yield prostaglandins (PGs) and thromboxanes (TXs), or via the lipoxygenase pathway to yield leukotrienes.

Figure 7

ARACHIDONIC ACID METABOLISM*



* From Valone, Boggs and Goetzl, Lipid Mediators of Hypersensitivity and Inflammation in *Allergy-Principals and Practice*, 1993. CO=cyclooxygenase, LO=lipoxygenase (Ref 104).

Cyclooxygenase catalyzes the incorporation of oxygen into arachidonic acid yielding the unstable intermediate, prostaglandin G_2 which is subsequently transformed into prostaglandin H_2. PGH_2 is then converted into **prostacyclin (PGI_2)**, **thromboxane (TXA_2)** and the primary prostaglandins, **prostaglandin D_2 (PGD_2)**, **prostaglandin E_2 (PGE_2)**, and **prostaglandin $F_2\alpha$ ($PGF_2\alpha$)** by a variety of enzymatic pathways that are highly cell-specific (105-107).

The most abundant cyclooxygenase product of human mast cells is PGD_2. While it acts similarly to histamine, it acts independently of histamine receptors. In the lung, PGD_2 acts to produce bronchoconstriction and pulmonary artery vasoconstriction while systemic release of this mediator causes marked hypotension (108). A metabolite of PGD_2 has been detected in the urine of patients with systemic mastocytosis but not that of normal persons (108). That PGD_2 played a role in generating hypotension in these patients was suggested when marked clinical improvement was demonstrated after the administration of aspirin, an inhibitor of PGD_2 generation. An interesting, but unexplained observation, is the finding that patients with systemic mastocytosis and high levels of mast cell activation experience rhinorrhea, bronchorrhea and urticaria, but not bronchoconstriction.

PGD_2 has several other functions, as well. It is chemokinetic for human neutrophils (109), it potentiates LTB_4-mediated accumulation of neutrophils in the skin (110), and it augments histamine release from human basophils (111). In addition, PGD_2, like PGI_2, inhibits the aggregation of human platelets (112). Inhibitors of PGD synthetase and the receptor for PGD_2 are being developed and may prove clinically useful for inhibiting the effects of this mediator *in vivo* (113).

Metabolism of arachidonic acid may also occur by a variety of lipoxygenases. These enzymes are a family of cytosolic enzymes that exhibit prominent cell specificity. The three major mammalian lipoxygenase enzymes are designated 5-, 12- and 15-lipoxygenase based upon the location of the carbon atom of arachidonic acid at which a molecule of oxygen is introduced. In neutrophils, mononuclear phagocytes, and mast cells the 5-lipoxygenase pathway is the primary pathway operative and it leads to the formation of 5-hydroxy-eicosatetraenoic acid (5-HETE) and the **leukotrienes**. The initial product, 5-hydroperoxy-eicosatetraenoic acid (5-HPETE), is first converted to an unstable intermediate, **leukotriene A_4 (LTA_4)** and then to **leukotriene B_4 (LTB_4)** and the **leukotrienes C_4, D_4, and E_4** (formerly termed the slow-reacting substance of anaphylaxis).

The *in vivo* effects of the leukotrienes are numerous. Three of their major functions include contraction of smooth muscle, mediation of bronchoconstriction and stimulation of airway mucous and electrolyte secretion. When lung tissue of asthmatics is stimulated by allergen *in vitro*, the course and magnitude of the resulting bronchoconstriction has been attributed to the large quantities of LTC_4, LTD_4, and LTE_4 that are produced. This effect can be abolished by pretreatment of the tissue with inhibitors of the 5-lipoxygenase pathway but not with inhibitors of cyclooxygenase demonstrating that the leukotrienes are more potent mediators of airway smooth muscle contraction than are the cyclooxygenase products (114). Leukotriene antagonists are in the process of development for human use and should allow a more clear assessment of the role of leukotrienes in airway pathophysiology.

Another potent newly-generated mediator, **platelet activating factor (PAF)**, is an ether-linked phospholipid with the general structure alkylacetyl-glyceryletherphosphorylcholine (AGEPC). While it was initially discovered as a proaggregatory, basophil-derived mediator of anaphylaxis in the rabbit, PAF is now known to be a product of many cell types and has a broad spectrum of activities (115,116) including bronchoconstriction. The role that PAF plays in mast cell mediated disease remains unclear. While purified human lung mast cells do produce PAF with stimulation, little of this is released from cells (117).

Mast Cell Cytokines

Until the last several years, the participation of mast cells in both physiologic and pathophysiologic events was thought to be solely dependent upon their preformed and newly generated mediators. It is now clear that mast cells are also capable of synthesizing cytokines, another class of mediators that play a pivotal role in the pathophysiology of allergic and immunological diseases.

Cytokines are proteins or glycoproteins that are synthesized and secreted by a variety of cells. The first categories of cytokines discovered were the interleukins, the interferons and colony stimulating factors. Generally, cytokine gene induction occurs in response to cellular injury or activation and the cells that produce them are widely distributed in the body. The biological effects are mediated by specific cytokine receptors located on the surface of target cells and include participation in cell growth, repair, inflammation and modulation of the immune response. Each cytokine molecule has multiple functions and often, more than one cytokine may possess a particular bioactivity (118). Importantly, cytokines do not act in isolation. They are involved in an intimate highly regulated network where they influence each other as well as numerous other biological processes (119).

Figure 8

SPECTRUM OF CYTOKINE FUNCTIONS*

Stem cell colony-stimulating factors
Lineage-specific cell growth and/or differentiation
Induction of MHC antigens
Cellular activation
Initiation of the acute-phase response
Enhancement of endothelial/leukocyte/lymphocyte adhesion
Promotion of chemotaxis
Modulation of cellular biological activities
    Transcriptional induction
    Arachidonic acid metabolism
    Protein phosphorylation
Cytotoxic/tumoricidal activity
Antiviral activity
Induction of other cytokines and/or cytokine receptors

*From Costa et al., Mast Cell Cytokines in *The Mast Cell in Health and Disease*, 1993 (Ref 120).

The initial reports of mast cell cytokine production occurred in 1987 when it was found that rodent mast cells were found to express IL-4 mRNA (121) and a cytolytic factor thought to be tumor necrosis factor (TNF-α) (122). More recently, activated mast cells have been shown to transcribe macrophage inflammatory proteins 1-α and 1-ß (MIP 1-α, MIP 1-ß), monocyte chemotactic and activating factor (MCAF), IL-1,2,3,4,5,10, granulocyte/macrophage colony stimulating factor (GM-CSF), transforming growth factor-ß (TGF-ß) and interferon-gamma (IFN-γ) while they constitutively transcribe TNF-α and IL-6 (123). Preliminary studies suggest that rodent mast cell lines also express mRNA for SCF and possess membrane-bound SCF (40). In marked contrast to the immediate release of the preformed mediators and the release within minutes of arachidonic acid metabolites, induction of cytokine synthesis by mast cells occurs hours after mast cell activation.

While most of the cytokine studies have been conducted in rodent mast cells, human mast cells have also been shown to participate in cytokine synthesis and release. Human lung mast cells have been shown to produce IL-4 and human skin mast cells, both TNF-α and IL-4 (124-126). However, the physiologic role played *in vivo* by these mast-cell derived cytokines remains speculative. Treatment of cultured human skin with mast cell degranulating agents has resulted in the appearance of the endothelial adhesion molecule ELAM-1 on the adjacent microvasculature (125). The fact that this response could be blocked by pretreatment of the cultures with mast cell stabilizing drugs, as well as with antibodies to TNF-α, is consistent with a model in which IgE-mediated production and release of TNF-α stimulates the dermal endothelium to express an adhesion molecule that is important for endothelial-leukocyte interactions.

Using skin blister chambers, several investigators have shown that, upon antigen challenge of atopic individuals, IL-1ß, IL-3, GM-CSF, and IL-6 appear in blister fluid within 12 hours after challenge (127-129). In addition, increased cell numbers expressing mRNA for IL-3, IL-4, IL-5, and GM-CSF have been detected in allergen-challenged skin of atopic individuals (130). While it has not been proven that mast cells are the source of these cytokines, it is highly likely that they are contributors since it is known that the cutaneous late-phase reaction is generated after mast cells have been triggered by IgE-dependent mechanisms.

In light of its ability to produce multifunctional cytokines the mast cell can no longer be thought of as a simple effector cell. Its functions have expanded to include an important regulatory role of both the inflammatory and immune responses. However, it is important to recognize that, to date, most of the studies examining cytokine production by mast cells have been performed using rodent mast cell lines or primary mast cell cultures. The extent to which human mast cells produce and secrete cytokines remains to be determined.

Figure 9

CYTOKINES PRODUCED BY MAST CELLS AND BASOPHILS*

Cell type	Cytokines	
	mRNA	Protein
Human		
Mast cells	TNF-α IL-4	TNF-α IL-4
Basophils		TNF-α IL-4
Rodent mast cells	TNF-α GM-CSF TGF-β SCF IFN-γ MIP-1α,β MCAF IL-1,2,3,4, 5,6,10	TNF-α IL-1,3,4,6

* From Schwartz and Huff, Biology of Mast Cells and Basophils in *Allergy-Principles and Practice*, 1993 (Ref 40).

Mast Cell Activation

Activation of mast cells immunologically involves the cross-linkage, by multivalent allergen, of IgE that is bound to the high-affinity Fcε receptor (FcεR1). This receptor contains four polypeptide chains, an α-, a β-, and two γ chains with the α-chain possessing the IgE binding site. Aggregation of as few as 1% of the 10^4 to 10^6 FcεR1 present per mast cell (131-133) results in exocytosis and the generation of newly-formed mediators. A number of sequential steps occur in exocytotic process. First, the granule swells as a result of the solubilization of the granule contents. This is followed by fusion

of the granular and plasma membrane and finally, expulsion of the granule contents.

Activation may also occur by nonimmunological means. It has been shown that human skin mast cells, unlike those from the lung, adenoid, tonsil or large intestine, release histamine after stimulation with substance P, VIP, somatostatin, compound 48/80, and morphine. Of interest, this reactivity does not parallel the phenotyping based on neutral protease content since intestinal mast cells, consisting of large numbers of the MC_{TC} subpopulation, are unresponsive to neuropeptide stimulation (134).

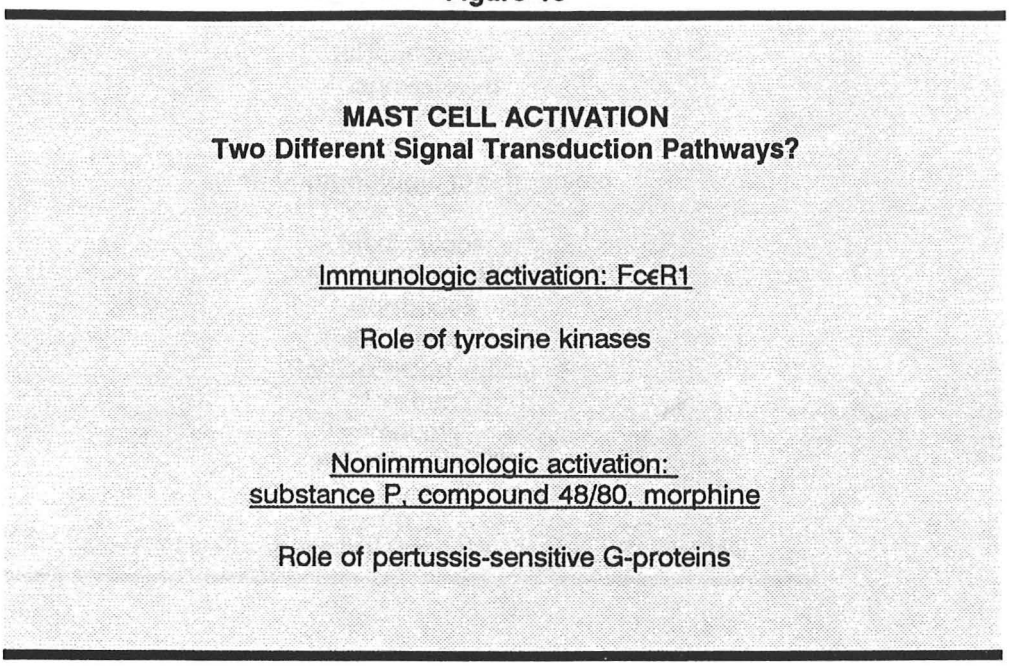
Recently, it has been shown that there are important differences between IgE-dependent and neuropeptide-induced mast cell activation. Degranulation by an IgE-dependent mechanism is a relatively slow process (occurring over 5 minutes) and results in the release of preformed mediators and the generation of the newly-formed mediators PGD_2 and LTC_4. In contrast, neuropeptide stimulation is rapid (occurring within 15 seconds) and leads to the release of preformed mediators only; PGD_2 and LTC_4 are not produced. When viewed by electron microscopy the degranulation process induced by immunological and nonimmunological activation appears identical. However, it is now known that the biochemical mechanisms involved in these two types of activation differ.

Enzymes that cause protein phosphorylation and dephosphorylation play an important role in signal transduction pathways linked to activation of cell surface receptors. Tyrosine and serine/threonine kinases and phosphatases all are important in regulating the events involved in cell growth and activation (135-138). Recently, it has been shown that tyrosine kinase is activated in RBL-2H3 rat mucosal mast cells resulting in the phosphorylation of a variety of proteins (139). Upon phosphorylation these proteins then bind to various intracellular signaling proteins. The importance of tyrosine kinase activity to coupled activation-secretion was demonstrated by the finding that inhibition of tyrosine kinase activity caused decreased histamine release in mast cells stimulated through FcεR1 (139-141). In contrast, if stimulation does not involve FcεR1 (nonimmunological stimulation), inhibition of tyrosine kinase does not diminish histamine release, while inhibition of GTP-binding proteins by pertussis toxin does (142-144). These results together suggest that signal transduction may occur by two different pathways depending upon the signalling source. Activation through FcεR1 appears to be associated, either directly or indirectly, with tyrosine kinase activation, while activation by neuropeptides and other nonimmunologic activators is initiated through a pertussis-sensitive G-protein.

When crosslinked by antigen, both the T cell receptor (TCR) and the FcεR1 on mast cells deliver an activation signal to their respective cells. This signal is mediated, in part, by the ζ chain of the T-cell receptor and by the γ chain of FcεR1. While these chains are encoded by different genes they are very similar in function. In fact, transvection studies have revealed that these two chains can be interchanged without loss of function. In addition, some T cells, including immature thymocytes, have been found to express the γ chain of the FcεR1 (145,146). Thus, it appears that Burnet (9,10)

may not have been wrong. Mast cells and T cells, indeed, may be related developmentally.

Figure 10



Mast Cell Secretagogues

In addition to activation by IgE, mast cells undergo receptor-mediated activation by the anaphylatoxins C3a, C4a and C5a (147). In addition, numerous other agents, with potential relevance to human disease, possess the capability of activating mast cells through nonimmunological mechanisms. Included in this group are: opioids (148), neuropeptides, drugs such as polymyxin B, amphotericin B, D-tubocurare, succinylcholine and iodinated contrast media (149), adenine nucleotides (150), hormones (151,152), and various physical stimuli (153,154). Also, inflammatory-cell-derived histamine releasing factors have been demonstrated to cause histamine release from human mast cells (Reviewed in 155). Thus, it appears that mast cells not only play a central role in allergic diseases and mastocytosis. The existence of numerous endogenous mast cell secretagogues suggests that these cells play an important role in normal physiologic processes as well.

Figure 11

MAST CELL SECRETORY AGONISTS

Immunologic mechanisms

IgE-mediated
Anaphylatoxins
Lymphokines

Non Immunologic mechanisms

Medications
Adenine Nucleotides
Hormones
Neuropeptides
Radiocontrast media
Dextran
Venoms
Physical Stimuli

* adapted from Tharp, Medical Grand Rounds, July 1984 (Ref 156).

Clinical Manifestations of Mast Cell Secretion

Mast cell mediator release results in a variety of clinical manifestations. As Tharp (156) stated in Internal Medicine Grand Rounds in 1984, the signs and symptoms expressed "are dependent upon several variables that include: 1) the anatomical location and number of tissue mast cells stimulated, 2) the extent and type of mediators released by the cells, and 3) the portal of entry, concentration, and nature of the potential mast cell agonist." Rate of antigen presentation and efficiency of cross-linking of mast cell bound IgE determine whether or not the cell will be triggered to release its mediator contents. In addition, in nonanaphylactic states, the clinical symptoms will reflect the anatomic location of mast cell activation. Therefore, while air-borne allergens cause upper and lower respiratory tract symptoms, orally-ingested allergens often elicit symptoms in the gastrointestinal tract alone. Like patients with immediate hypersensitivity reactions, patients with mastocytosis often present with a constellation of symptoms reflective of mast cell activation at several anatomic sites.

Figure 12

CLINICAL MANIFESTATIONS OF MAST CELL SECRETION*

Anatomical Region	Clinical Manifestations
Upper Respiratory Tract	Congestion, rhinorrhea, laryngeal edema, hoarseness
Lower Respiratory Tract	Dyspnea, wheezing, cyanosis
Eye	Lacrimation, pruritus, suffusion
GI Tract	Nausea, vomiting, abdominal cramps, diarrhea
Heart	Tachycardia, arrhythmia, angina (?)
Skin	Pruritus, pain, flushing, urticaria, angioedema
Neurological	Headache, dizziness, syncope

*From Tharp, Medical Grand Rounds, 1984 (Ref 156).

MASTOCYTOSIS

Mastocytosis is a rare disease that is characterized by increased mast cell numbers in the skin and other organs. As stated by Tharp (156), mastocytosis "represents a spectrum of clinical disorders that vary in regard to patient age, to the predominant clinical manifestations, and to the nature and extent of the mast cell proliferative process." Many patients have a benign, indolent form of the disease and, when properly medicated, live relatively normal lives. Others have a more aggressive form and, for these individuals, the prognosis is not so optimistic. The organ most frequently involved is the skin (cutaneous mastocytosis). However, many other organ systems may be involved, as well, including the liver, spleen, lymph nodes, gastrointestinal tract, bone marrow and skeletal systems. A myriad of symptoms occur, and these may be either localized to the organ system involved or systemic depending upon whether there is local or generalized mast cell mediator release.

While mastocytosis may occur at any age, in approximately 55% of cases, the onset is between birth and two years of age. Another 10% develop symptoms between ages two through fifteen, and 35% present with the disease in adulthood (157). The prevalence of disease is unclear and familial occurrence is not common. Both the manifestations of mastocytosis, as well as its prognosis, are dependent upon when the disease presents. Children typically present with cutaneous lesions, the most frequent being a solitary mastocytoma and urticaria pigmentosa. Less commonly they will present with diffuse cutaneous mastocytosis (158) and rarely, telangiectasia macularis eruptiva perstans (TMEP) which is often the presenting symptom in adults (157). The majority of children have cutaneous disease alone and the prognosis for these patients is quite good. Half of these children will experience resolution by adolescence and the remainder will experience a marked reduction in symptoms (159). In a minority of children the disease persists into adulthood, and, like patients with the adult-onset form of the disease, these individuals more commonly experience systemic involvement.

Etiology

The cause of increased mast cell accumulation in the skin and other organs has not been identified. While several hypotheses have been generated none have been confirmed. It has been postulated that the disorder may result from the development of a neoplastic clone. However, clinical observations have not supported this theory. In children with mastocytosis the disease is often self-limited with complete resolution commonly occurring by adolescence. In addition, despite frequent persistence of the adult-onset form throughout life, these patients rarely die from a neoplastic mast cell process. Moreover, the mast cells of these patients usually appear normal by transmission electron microscopy (156).

Critical to the growth and development of mast cells is an array of cytokines that are elaborated by various cell types. Recently, it has been shown that altered metabolism of one of these cytokines, mast cell growth factor (stem cell factor, c-*kit* ligand), may be the etiology of cutaneous mastocytosis in some patients with this form of the disease (160). In addition to stimulating the growth and differentiation of murine mast cells *in vitro* (11,18,20-23), mast cell growth factor causes the accumulation of these cells into the skin after dermal injection (17,161). To determine the role of this factor in mastocytosis Longley and colleagues (160), using immunohistochemical techniques and the polymerase chain reaction, looked for the expression of the mast cell growth factor gene in the skin of patients with cutaneous mastocytosis.

As demonstrated previously in Figure 1, mast cell growth factor exists in two forms, a membrane-bound form and a soluble form (18, 23, 162-165). Normally, the soluble form is produced from the membrane-bound form by proteolytic cleavage at a protease-sensitive site (18,23,162-165) that is encoded by a particular region of the gene known as exon 6. This segment of the gene may be present in the final mRNA or it may be deleted in the primary gene transcript due to alternative splicing. Therefore, in order

to produce the soluble form of this factor, both a full-length mRNA must be present as well as a functional protease.

Upon examining normal skin immunohistochemically for the presence of mast cell growth factor, Longley and colleagues (160) found that, while a small number of dermal fibroblasts, dendritic cells and resident mast cells stained positive for the presence of mast cell growth factor, keratinocytes stained to the greatest degree. The pattern of staining was diffuse and granular consistent with the presence of intracellular and membrane-bound forms of the protein. In contrast to the skin of normal subjects, the skin of patients with cutaneous mastocytosis demonstrated abundant immunoreactive mast cell growth factor, not cell-associated, but present in the extracellular spaces, between keratinocytes and free in the papillary dermis. In addition, it was found that there were no sequence abnormalities detected in the mRNA for mast cell growth factor in the one patient studied. Thus, it was concluded that the altered distribution of mast cell growth factor in the skin of patients with cutaneous mastocytosis results from abnormal production of the soluble form of this factor, possibly due to increased proteolytic processing. These findings add support to the hypothesis that mastocytosis results from an abnormal proliferation of mast cells and not from mast cell neoplasia.

Classification schemes

Classification of a disease as heterogeneous as mastocytosis is difficult. In most schemes, cutaneous mastocytosis has been separated from systemic mast cell disease (SMCD), and is described according to the distribution or the morphology of the cutaneous lesions. The characterization of systemic mastocytosis has been based upon the distribution of organ involvement, and upon the nature of the process, i.e., "benign" or "malignant" (166).

Most of the original proposed schemes categorized mastocytosis into "benign" and "malignant" forms and, have not allowed for comparisons to be made between descriptions of mastocytosis in articles from different authors. While "malignant" may be used by one author to describe a patient with systemic mastocytosis that has persisted for many years and that has caused severe gastrointestinal disease, another may use the term to describe a patient who has had the disease for only a few months but who has a rapidly progressive form of the disease. As Metcalfe stated recently in a roundtable discussion on mastocytosis, "Clearly, such definitions do not allow categorization for treatment and for assignment of prognosis." (166)

As knowledge regarding the disease process has improved, it has been realized that mastocytosis may be associated with several clinical conditions that, because of their severity, often predict the disease course. These associated diseases include various myeloproliferative disorders and mast cell leukemia (167). In 1988 a classification scheme incorporating these disease associations was proposed. An extensive study by Travis and colleagues (168) was designed to identify features

important in predicting survival in patients with systemic mastocytosis and findings from it led to the formation of a classification scheme that continues to be useful today. A slightly modified version (166) is presented in Figure 13.

Figure 13

CLASSIFICATION OF MASTOCYTOSIS

I. Indolent mastocytosis

   A. Skin only
      Urticaria pigmentosa
      Diffuse cutaneous mastocytosis
      Mastocytoma
      Telangiectasia macularis eruptiva perstans

   B. Systemic (± urticaria pigmentosa)
      Bone Marrow
      Gastrointestinal

II. Mastocytosis with an associated hematologic disorder (± urticaria pigmentosa)
   A. Dysmyelopoietic disorders
   B. Myeloproliferative disorders
   C. Acute non-lymphatic leukemia
   D. Malignant lymphoma
   E. Chronic neutropenia

III. Mast cell leukemia

IV. Lymphadenopathic mastocytosis with eosinophilia (± urticaria pigmentosa) (aggressive mastocytosis)

As shown in Figure 13, the terms "benign" and "malignant" are not included in the revised classification scheme because the distinction between these two forms of the disease may not always be clear-cut. The term "indolent" was adopted to describe patients with favorable prognostic features. While this term suggests that individuals in this category will have a favorable prognosis, it also allows for the possibility that some of the patients in this category may develop severe symptoms or experience a transformation of their disease into a more aggressive form (168).

Patients that, in the past, fell into the "malignant" category have been separated on clinical or pathologic criteria into three groups, all characterized by a rapid disease

course: 1) SMCD with associated hematologic disorders, 2) mast cell leukemia and 3) aggressive SMCD. Travis and colleagues (168) found that, in the SMCD patients with an associated hematologic disorder (those in category II), poor prognosis was more associated with the hematologic disorder than with the SMCD. For that reason, the term "malignant", which suggests that poor prognosis results from the malignant proliferation of mast cells was dropped.

It has been recognized for many years that most patients in the indolent category have urticaria pigmentosa or diffuse cutaneous mastocytosis at some time in their disease. In contrast, the presence of cutaneous disease in patients in categories II through IV is variable. Moreover, it has been noticed if the disease evolves into a leukemic process, urticaria pigmentosa, if present, is sometimes lost (166).

It is important to realize that, despite the prognostic category, the signs and symptoms of mastocytosis are similar and are related to the release of preformed and newly-generated mast cell mediators. Therefore, patients of all categories may experience pruritus, anaphylaxis and eventually, other problems resulting from specific organ involvement. In some instances, however, morbidity and, ultimately, mortality may be dependent upon direct mast cell infiltration as opposed to mediator release.

Since the 1988 classification scheme was proposed by Travis et al. (168), a slightly revised classification was developed in a consensus conference in 1991 and is presented in Figure 14. As shown, the major categories are the same. The only major change is that the potential organs involved in systemic disease in category I are listed (169).

Figure 14

Revised Mastocytosis Classification

I. Indolent mastocytosis

- A. Syncope
- B. Cutaneous disease
- C. Ulcer disease
- D. Malabsorption
- E. Bone marrow mast cell aggregates
- F. Skeletal disease
- G. Hepatosplenomegaly
- H. Lymphadenopathy

II. Hematologic disorder

- A. Myeloproliferative
- B. Myelodysplastic

III. Aggressive

Lymphadenopathic mastocytosis with eosinophilia

IV. Mastocytic leukemia

Cutaneous Mastocytosis

Urticaria pigmentosa - In any form of mastocytosis the organ most frequently involved is the skin and, the most frequent cutaneous lesions are those of urticaria pigmentosa. While the lesions usually appear early in life, they may occur in adolescence and in adulthood as well. They appear as discrete reddish-brown macules and papules, and they occur in a randomized and generalized distribution. The presence of Darier's sign (urtication upon stroking due to mast cell degranulation) is a confirmatory sign for the presence of mast cell infiltrates in the skin. Associated symptoms include pruritus and dermographism. However, more severe symptoms may occur if there is extensive cutaneous involvement (170-172). The lesions commonly occur on the trunk, but any area of the skin may be affected, including the mucous membranes. The palms, soles, face, and scalp are usually spared. In infants the lesions are often bullous because tissue edema causes the skin to separate at the poorly formed dermal-epidermal junction (173,174, reviewed in 175).

The number of patients with urticaria pigmentosa that actually have systemic disease remains unclear. Upon evaluating 35 patients with cutaneous lesions alone, Czarnetzki et al. (176) found that 46% had focal mast cell accumulation in the bone marrow. In other studies a range of 10 to 70% has been described (159,177). More recently, it has been suggested that the presence or absence of bone marrow involvement in urticaria pigmentosa may be related to mast cell burden. With few cutaneous lesions there may be no bone marrow involvement, whereas with many lesions bone marrow involvement is more likely (Metcalfe, personal communication).

The prognosis for patients with urticaria pigmentosa depends on the age of onset of the skin lesions. While the majority of children demonstrate marked improvement or total resolution by adolescence or adulthood (159,178), the disease course for adults is less clear. Generally, adults with urticaria pigmentosa have chronic disease and a greater chance of eventual systemic involvement (179).

Mastocytoma - These appear at birth or shortly thereafter (180) as solitary or multiple macules, plaques, or nodules. Most mastocytomas occur on the extremities, but not on the palms or soles. As with urticaria pigmentosa the lesions may urticate with stroking. The prognosis for patients with mastocytomas is very good. In many instances, the lesions either spontaneously involute or improve markedly after several years (159,181).

Diffuse cutaneous mastocytosis - This rare form of cutaneous mastocytosis generally affects children before the age of three. The skin, which is diffusely involved, often takes on a red-yellow-brown color. An erythrodermic form is characterized by diffuse edema and thickening of the skin (173,175). Infants may first present with extensive bullae prior to the development of diffuse cutaneous mastocytosis. Thus, this condition should be included in the differential diagnosis of neonatal blistering diseases (182). While this form of cutaneous mastocytosis usually resolves before age five, these children are at risk of developing flushing, hypotension, shock, and death (175).

Telangiectasia Macularis Eruptiva Perstans (TMEP) - This form of cutaneous mastocytosis occurs primarily in adults. The lesions consist of generalized, red, telangiectatic macules on a tannish-brown background. Generally, they are smaller than the lesions associated with urticaria pigmentosa and are not pruritic (175). The prognosis for patients with TMEP is similar to that of patients with urticaria pigmentosa.

Histopathology and Diagnosis - The diagnosis of cutaneous mastocytosis should be confirmed by biopsy. In urticaria pigmentosa increased mast cell accumulation is seen in the papillary dermis and, in some instances, throughout the entire dermis. In TMEP mast cell accumulation is most prominent around the capillary venules of the superficial plexus. While nonlesional skin may have modestly increased mast cell numbers, lesional skin contains the greatest accumulations. Usually, a fifteen to twenty-fold increase is noted. However, it is important to realize that increased mast cell

numbers alone is not sufficient to make the diagnosis of cutaneous mastocytosis. Numerous other skin diseases have been associated with increased mast cell numbers as well. However, these diseases are easily differentiated from mastocytosis by other distinguishing characteristics (Reviewed in 156).

Mast cells in the skin are identified using metachromatic stains or the conjugated avidin technique (183). Analysis of the granule ultrastructure of the mast cell granules reveal a predominance of grating/lattice structures indicating that these cells are of the MC_{TC} variety (55). More recently, a study using a combination of electron microscopy and morphometric analysis showed that there may be quantitative differences between the mast cells from patients with systemic disease and those from patients with cutaneous involvement alone. Cutaneous mast cells from lesional skin of individuals with systemic disease had a larger mean cytoplasmic area, nuclear size, and granule diameter than those from adults with non-systemic disease (185).

In patients with urticaria pigmentosa and systemic disease mean levels of histamine and tryptase have been shown to be elevated, whereas they have not in patients with cutaneous disease alone (70,186). In light of the difficulty in making accurate histamine determinations and the fact that the majority of histamine is excreted as the metabolite, 1-methyl-4-imidazoleacetic acid (MeIMAA), this marker is helpful in identifying patients with mastocytosis. MeIMAA levels have been shown to be elevated in the majority of patients with systemic disease as well as in those with cutaneous disease alone (187).

Treatment - An important component of treatment of patients with cutaneous mast cell disease is the avoidance of factors that may trigger mediator release. Potential triggers include: temperature changes, friction, physical exertion, ethanol ingestion, and the use of nonsteroidal anti-inflammatory agents or opiates (175). In addition, it has been demonstrated that patients with urticaria pigmentosa are more predisposed to developing anaphylaxis following Hymenoptera stings despite the absence of antigen-specific IgE (188).

In children with an isolated mastocytoma, surgical removal may be necessary if spontaneous involution does not occur. Patients with urticaria pigmentosa who experience pruritus and whealing benefit from treatment with H1 antihistamines alone or in combination with H2 antihistamines (189). In addition, disodium cromoglycate and ketotifen also have been shown to be effective in some studies (190-194). More recently, a platelet-activating factor antagonist was shown to reduce pruritus and flushing in an adult with urticaria pigmentosa and systemic disease (195).

Another mode of therapy, psoralen plus ultraviolet A photochemotherapy (PUVA), has been shown to decrease both the symptoms associated with urticaria pigmentosa as well as the lesions themselves. However, relapses often occur after the cessation of therapy (196-199). Therefore, because of its possible side effects and transient benefit,

this form of therapy should be used only in refractory cases. Finally, while systemic corticosteroids have not been effective in treating cutaneous mastocytosis, the application of a potent topical corticosteroid under occlusion has had promising results (200).

Figure 15

TREATMENT OF CUTANEOUS MASTOCYTOSIS*

Mastocytoma

Excision if no resolution.

Urticaria pigmentosa and Diffuse/Erythrodermic Cutaneous Mastocytosis

H1 antihistamines
H1 and H2 antihistamines
Ketotifen
Disodium cromoglycate
Topical corticosteroids with occlusion
Ultraviolet B phototherapy
Psoralen plus ultraviolet A photochemotherapy (PUVA)

Telangiectasia macularis eruptiva perstans

Unknown

* Adapted from Soter, J Invest Dermatol 96:32S, 1991 (Ref 175).

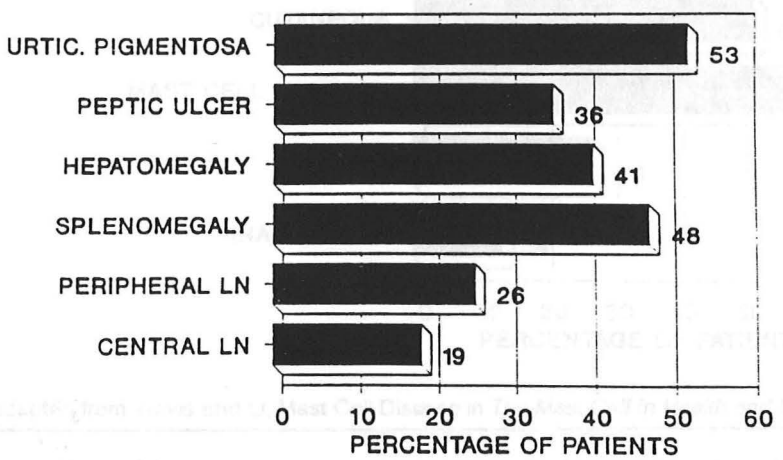
Systemic Mastocytosis

Systemic mastocytosis is characterized by an abnormal proliferation and accumulation of mast cells in the bone marrow, spleen, liver, skin, bone, and lymph nodes. While children may develop SMCD, the incidence in adults is much greater. Affected patients are usually between the ages of 50 and 80.

The percentage of patients with cutaneous lesions varies from 50% to 100% depending upon the pattern of referral (168). Travis et al. (168), in an extensive analysis of 58 patients with SMCD, found that 53% had cutaneous disease. An even greater percentage (86%) was found by Horan and Austen (201) in a retrospective ten year review at Brigham and Women's Hospital. Involvement of other organs is variable. Travis et al. (168) found hepatomegaly in 41% of the cases examined, splenomegaly in 48%, peptic ulcer in 36% and peripheral and central lymphadenopathy in 26% and 19%, respectively. While the bone marrow was not examined in the Mayo Clinic study, Horan and Austen (201) found bone marrow involvement in 73% of the 21 patients they evaluated.

Figure 16

ORGAN INVOLVEMENT IN SYSTEMIC MASTOCYTOSIS*
The Mayo Clinic Experience
1954-1985



* Adapted from Travis and Li, Mast Cell Disease in *The Mast Cell in Health and Disease*, 1993 (Ref 202).

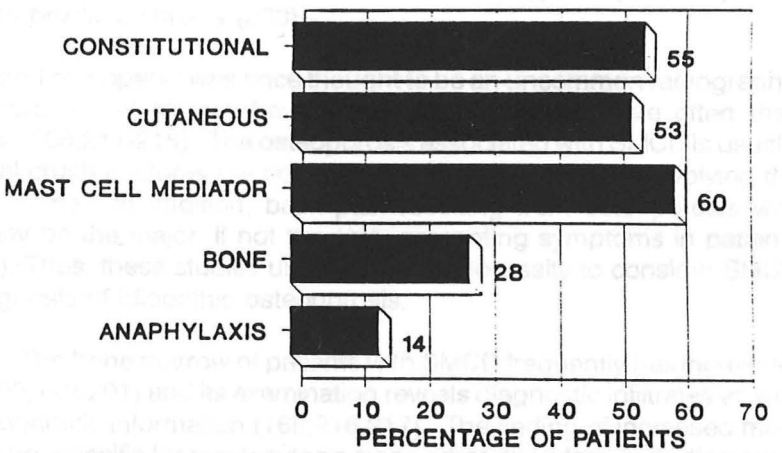
For many patients with SMCD the course is relatively benign and the prognosis is good. However, patients with a more malignant form of the disease, characterized by marked mast cell proliferation and widespread organ involvement often experience a fatal outcome.

Clinical Presentation

Patients with SMCD experience a myriad of signs and symptoms and these were categorized into five major groups in the Mayo Clinic study (168). Constitutional symptoms (fatigue, weight loss, fever and sweats) were experienced by 55% of the patients studied. Cutaneous manifestations (urticaria, pruritus and dermatographism) were experienced by 53%, while symptoms of mast cell mediator release were seen in 60%. The predominant symptoms associated with mediator release in this study included abdominal pain, respiratory symptoms, diarrhea, nausea, vomiting, flushing and syncope and, unless there was underlying asthma, the respiratory symptom experienced by most patients was dyspnea, not wheezing. Bone manifestations consisting of bone pain, arthralgias and fractures were seen in 28% and anaphylaxis occurred in 14%.

Figure 17

SIGNS AND SYMPTOMS OF SYSTEMIC MAST CELL DISEASE*
The Mayo Clinic Experience
1954-1985



* Adapted from Travis and Li, Mast Cell Disease in *The Mast Cell in Health and Disease*, 1993 (Ref 202).

Most of the symptoms experienced occur during discrete episodes, and these are often described as "attacks" by the patient. These episodes, which may be brief or prolonged, coincide with the sudden release of mast cell mediators and can be triggered by heat, exertion, emotional upset, or certain pharmacologic agents. The patient initially feels warm and is flushed. Subsequently, he or she experiences palpitations and lightheadedness which are attributed to systemic vasodilation. Dyspnea, nausea, abdominal cramping, vomiting and diarrhea occur variably among patients.

Organ Involvement

Skin - The skin manifestations seen in SMCD are similar to those seen in isolated cutaneous disease. Urticaria pigmentosa, the most common cutaneous manifestation, is seen in over 90% of patients with indolent disease, but in less than 50% of patients with an associated hematologic disorder or aggressive disease (203). Other cutaneous patterns associated with SMCD include telangiectatic, pigmented macules (TMEP); erythroderma; diffuse, infiltrative plaques and nodules, and dermographism and flushing. Each of these are well-described in several extensive reviews (156, 175).

Bone - Approximately 60-70% of patients with SMCD develop radiographic bone lesions (168) with the most common abnormalities being diffuse, sclerotic and lucent areas involving the axial skeleton (179,204,205). Less frequently, focal osteoporotic/osteosclerotic lesions are seen in the skull and long bones (179). Travis et al. (168) found the most common diffuse pattern to be demineralization (28% of patients) followed by osteosclerosis (19%). Mixed sclerosis and demineralization was seen in 10% of the patients studied. The pathophysiology of these skeletal abnormalities is thought to be at least partially dependent upon the mediators produced by the mast cell. Both heparin and PGD_2 are known to cause bone resorption (206,207) while histamine is known to promote fibrosis (208).

While generalized osteopenia was once thought to be an uncommon radiographic finding (209,210), more recent studies have shown that it occurs more often than previously recognized (168,211-215). The osteoporosis associated with SMCD is usually very severe. Vertebral crush fractures are common and are often multiple involving the thoracic and lumbar spine. In addition, back pain resulting from osteoporosis with vertebral fractures may be the major, if not the sole, presenting symptoms in patients with SMCD (212-215). Thus, these studies underscore the necessity to consider SMCD in the differential diagnosis of idiopathic osteoporosis.

Bone marrow - The bone marrow of patients with SMCD frequently has increased mast cell numbers (103,179,201) and its examination reveals diagnostic infiltrates as well as provides useful prognostic information (168,216,217). The finding of increased mast cell numbers alone is not specific for mastocytosis since other disorders, including renal osteodystrophy, multiple myeloma, other malignancies, and common osteoporosis, may demonstrate increases as well. The diagnosis is usually not very difficult, however, since the magnitude of the increase is significantly greater in mastocytosis compared to that seen in the other disorders and the lesions are distinctive. The majority of the lesions are focal and in a paratrabecular location although they may be perivascular and parafollicular. The nodular aggregates consist of spindle-shaped mast cells often associated with lymphocytes and eosinophils. Early in the course of the disease the marrow lesions are cellular, while later in the course when the mast cell number decreases, the lesions become more fibrotic. Several important poor prognostic factors have been identified based upon bone marrow analysis and include: low percentage of

fat cells with a hypercellular marrow; existence of mast cells with lobulated nuclei; and presence of a hematologic disorder (168).

Figure 18

Adult Mast Cell Disease
Bone Marrow Involvement*

Series	No. of Patients	Focal Lesions	Focal/Diffuse Lesions
Webb	26	84%	100%
Brunning	14	82%	100%
Horny	38	92%	100%
Ridell	18	56%	56%
Travis	58	NA	NA

*From Parker, Hematologic Aspects of Mastocytosis. J Invest Dermatol 96(suppl):47S, 1991 (Ref 218).

Critical to the identification of mast cells in the bone marrow is the use of proper staining techniques. Often the metachromatic staining properties of the mast cell granules are lost during routine staining procedures due to the decalcification process. Optimal staining occurs when the biopsy specimen undergoes nondecalcified plastic embedding prior to staining with toluidine blue or other metachromatic dyes. Thus, in light of these requirements, it is important that the pathologist be consulted prior to the biopsy so that the sample is processed properly.

Various hematologic abnormalities have been demonstrated in patients with SMCD (103,168,179). These range from mild cytopenias and cytoses to premalignant and malignant syndromes. Anemia, the most common hematologic abnormality, occurs in a third to a half of patients with systemic disease, while thrombocytopenia and eosinophilia have been demonstrated in up to 25%. Both anemia and thrombocytopenia are significant indicators of poor prognosis. A significant number of patients with hypercellular marrows have other serious associated hematologic disorders including dysmyelopoietic syndromes, myeloproliferative disorders, leukemia, lymphoma and chronic neutropenia (216,219-222). These patients have a markedly reduced 5-year survival (168).

Figure 19

SYSTEMIC MAST CELL DISEASE
Hematologic Manifestations*

Cytopenias

Anemia
Thrombocytopenia
Leukopenia/granulocytopenia

Cytoses

Leukocytosis/granulocytosis
Eosinophilia
Monocytosis
Thrombocytosis
Lymphocytosis

*From Parker, Hematologic Aspects of Mastocytosis. J Invest Dermatol 96(suppl):52S, 1991 (Ref 223).

Liver - In the several studies in which it was examined, hepatomegaly occurred in 40%-72% of the patients studied (103,168,179,201,224,225). Despite this frequency of liver involvement, abundant pathological data is lacking. In the majority of patients with mastocytosis the liver, lymph nodes, and spleen are rarely biopsied unless there is significant organ dysfunction or a suggestion that a malignant process is occurring. For these reasons, the available data on mast cell accumulations in these organs is based primarily on data from patients with aggressive disease. A study of hepatic pathology in thirteen patients revealed hepatic fibrosis in all specimens examined (226). Fibrotic patterns included a periductal pattern and portal to portal fibrosis with fatty metamorphosis and sinusoidal dilatation also occurring in a significant number. A mononuclear cellular infiltrate was seen but inflammation was not prominent. Interestingly, excluding the alkaline phosphatase, the liver function studies were often normal despite extensive liver involvement.

Spleen - Splenomegaly is not an uncommon finding in SMCD. Travis et al. (168) found that 48% of the 58 patients they evaluated had an enlarged spleen while Horny et al. (227) demonstrated involvement in 72% of their patients. These percentages are similar to those that were obtained in three previous studies (103,179,224). Pathological

examination revealed mast cell infiltrates in a paratrabecular distribution with various degrees of trabecular fibrosis and eosinophilic infiltrates (228).

Lymph nodes - Lymph node involvement is less common than either hepatomegaly or splenomegaly. In the study by Travis et al. (168) peripheral lymphadenopathy was noted in 26% of 58 patients examined while central lymphadenopathy occurred in 19%. Pathologic evaluation revealed that mast cell infiltrates were most commonly found in the paracortex, followed by the follicles, medullary cords and the sinuses. These were accompanied by eosinophils. Lymph node involvement has been found to be more extensive in patients with either associated hematologic malignancies or aggressive non-leukemic mastocytosis (228,229).

Gastrointestinal tract - Gastrointestinal symptoms are common in patients with SMCD. Abdominal pain was seen in 35% of the patients evaluated by Travis et al. (168) and in 80% of the 21 patients retrospectively reviewed by Horan and Austen (201). GI symptoms were also seen in 80% of the 16 patients recently evaluated by Cherner et al. (230). Two different types of abdominal pain, dyspeptic and nondyspeptic, are generally described (201,230). The dyspeptic variety is often associated with increased acid secretion (secondary to stimulation by histamine) and peptic ulcer disease (168,230), while the nondyspeptic variety is not. Cherner et al. (230) found that 38% of their patients had gastric acid hypersecretion and 44% had evidence of peptic ulcer disease. Interestingly, increased acid hypersecretion and increased incidence of peptic ulcer disease had not been demonstrated in previous studies (231-233). The low incidence of these two findings in previous studies probably resulted from their underdiagnosis, not their absence. Cherner (230) also found that a significant number of patients (30%) experienced abdominal pain of the nondyspeptic variety. This pain was localized to the lower abdomen, was not relieved by H_2- receptor antagonists, and was not associated with abnormal radiographic findings or gastric acid hypersecretion.

Multiple factors may contribute to the GI abnormalities seen in systemic mastocytosis. The cause of abdominal pain may result from peptic ulcer disease (171,172,230), edema/urticaria of the GI tract or a motility disorder (171,172,231). Diarrhea, another frequent GI manifestation, appears to result from altered intestinal secretion, structural disease of the small intestine or a hypermotility/transit disorder (203). Malabsorption, caused by diffuse small intestinal mucosal dysfunction (230,232,233), may also be seen but is usually not severe.

Summary of Clinical Features

The spectrum of signs and symptoms at presentation may lead to an incorrect initial diagnosis. In fact, of the 58 patients evaluated by Travis et al (168), 80% were initially incorrectly diagnosed. Since systemic mastocytosis has a predilection for certain organs, it is important that this disease process be considered in patients presenting with unexplained bone, skin, hematologic, gastrointestinal and systemic manifestations.

Figure 20

INITIAL DIAGNOSIS IN SMCD PATIENTS AT MAYO CLINIC

Diagnosis	Number of Patients
Bone manifestations	
Osteoporosis	5
Metastatic carcinoma	4
Multiple myeloma	2
Paget disease	1
Gaucher disease	1
Skin manifestations	
Malignant melanoma	1
Rocky Mountain spotted fever	1
"Colored hives"	1
Hematologic manifestations	
Lymphoma	6
Acute leukemia	3
Chronic myeloid leukemia	3
Myelofibrosis	2
Myeloproliferative disorder	2
Neutropenia	1
Hypereosinophilic syndrome	1
Eosinophilic leukemoid reaction	1
ITP	1
Idiopathic splenomegaly	1
Gastrointestinal manifestations	
Irritable bowel	1
Primary biliary cirrhosis	1
Portal hepatitis	1
Systemic manifestations	
Diabetic shock	1
Carcinoid syndrome	1
Hypertension	1
Hypotension	1
Hypersensitivity vasculitis	1
Parasitic infection	1

Diagnostic Evaluation

The diagnosis of systemic mastocytosis is based upon multiple criteria. Clinical presentation, physical exam, laboratory analysis, radiographic findings and histologic findings all must be considered. Since the majority of patients present with skin manifestions the diagnosis is easily confirmed by skin biopsy. Again, it must be emphasized, that the specimen must be prepared and stained properly so that the mast cells can be identified. In addition, since small increases of cutaneous mast cells can be seen in other disorders, increased numbers alone is not sufficient. At least a ten-fold increase is usually seen (234, Metcalfe, personal communication). In the absence of cutaneous lesions, however, the diagnosis is more problematic. While a blind skin biopsy may be helpful by revealing increased mast cell numbers, usually the diagnosis requires a more extensive evaluation.

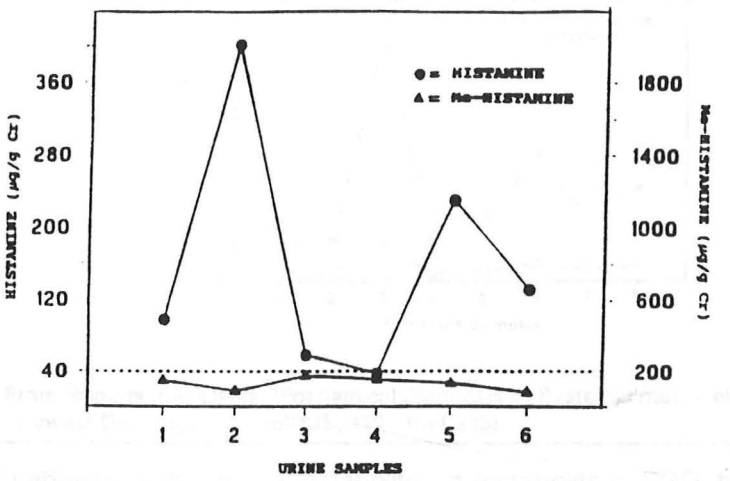
Numerous biochemical mediators are released upon mast cell activation, and their identification and quantitation can help to establish the diagnosis of SMCD. Again, the finding of increased mediator levels alone is not sufficient to establish a diagnosis since individuals with episodic mast cell activation, but no evidence of abnormal mast cell proliferation (i.e. those with anaphylaxis), may have increased mediator levels as well. However, one differentiating factor between these two groups is that mediator levels in patients with mastocytosis usually are chronically elevated while, in patients with anaphylaxis, they are elevated immediately after mast cell activation only. The mast cell secretory products most easily identified clinically are histamine and its metabolites, PGD_2, tryptase, and heparin (Reviewed in 235).

While numerous methods exist for measuring histamine in both serum and urine (236-239,reviewed in 235), many lack sensitivity, specificity and reproducibility (240-242). In addition to these difficulties, there are other significant problems associated with quantifying histamine in human biological fluids. Unless blood is collected carefully, artificial elevations of histamine may be found secondary to basophil histamine release. This problem may be reduced by using a calcium chelator such as EDTA as an anticoagulant to reduced basophil activation, but it often is not eliminated (235).

Other difficulties also exist when attempting to quantitate urinary histamine. Certain bacteria can decarboxylate histidine to histamine and, if these are present in sufficient quantities in the urinary tract, urinary histamine levels may be falsely elevated (187). By measuring histamine metabolites, N-methyhistamine and N-methylimidazole acetic acid (MeIMAA), this problem can be circumvented. While bacterial metabolism to histamine can occur, further metabolism does not. Therefore, while a normal individual may have elevated urinary histamine levels, the levels of histamine metabolites will be normal. As would be expected, this problem occurs more often in women since they are more predisposed to developing an overproliferation of urinary tract bacteria.

Figure 21

24-HOUR URINE COLLECTION FROM A NORMAL FEMALE
Histamine and N-methylhistamine levels*



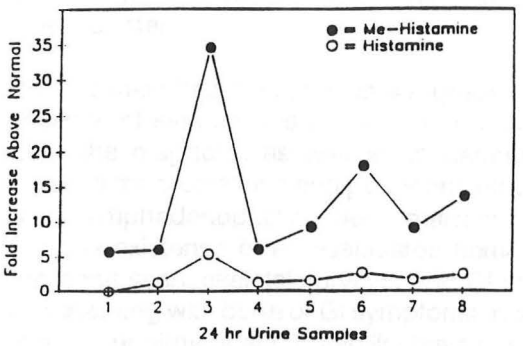
*From Roberts and Oates, Biochemical Diagnosis of Systemic mast Cell Disorders. J Invest Dermatol 96(suppl)19S, 1991 (Ref 235).

Urine histamine determinations also may not be an accurate diagnostic indicator of systemic mast cell activation in patients with SMCD due to altered histamine metabolism (187,243). In some patients, while elevated levels of histamine metabolites are present in the urine, the histamine level itself may be normal. Therefore, for all of the above reasons, urinary analysis of histamine metabolites, not histamine, should be performed on every patient suspected of have systemic mast cell disease.

Granerus et al. (243) in 1983 determined whether extent of disease involvement correlated with the amount of urinary histamine metabolites in 30 patients with mastocytosis. He found that patients with skin manifestations alone had low levels of urinary MeIMAA levels while those with extensive organ involvement had markedly elevated levels. Thus, urinary histamine metabolite analysis may also be useful in distinguishing between isolated cutaneous disease from more widespread systemic involvement as well as in the initial diagnosis of the disease itself.

Figure 22

24-HOUR URINE COLLECTION FROM A PATIENT WITH SMCD
Histamine and N-methylhistamine levels*



*From Roberts and Oates, Biochemical Diagnosis of Systemic mast Cell Disorders. J Invest Dermatol 96(suppl)19S, 1991 (Ref 235).

In addition to histamine metabolites, a metabolite of PGD_2 has also been found to be elevated in the urine of patients with SMCD. Using a mass spectrometric assay for the measurement of 9α-hydroxy-11, 15-dioxo-2,3,18,19, -tetranorprost-5-ene-1, 20-dioic acid Roberts (244) detected elevations of this metabolite in patients with proliferative mast cell disease. More recently, an assay for another PGD_2 metabolite has been developed and levels of this metabolite, as well, were found to be elevated and were shown to correlate with levels of N-methylhistamine in patients with SMCD (245). Unfortunately, neither of these assays are available for routine clinical use.

While heparin is a preformed mediator and is released during mast cell activation and secretion, adverse effects from this release are rarely noted. The partial thromboplastin time has been found to be elevated only during extensive mast cell activation (246,247). Therefore, for this reason, routine coagulation studies have not been recommended in the diagnostic evaluation of patients with suspected mastocytosis.

Probably the most useful indicator of mast cell activation is the presence of elevated plasma tryptase levels. As shown in Figure 6, elevations have been demonstrated in the majority of patients with mastocytosis and anaphylaxis, but not those with sepsis or myocardial infarctions (170). Interestingly, of the 17 mastocytosis patients evaluated six did not have elevated tryptase values. All of these had urticaria pigmentosa and mast cell involvement of one or more organs. However, because all were evaluated during a quiescent period (not during an "attack") mediators may not have been elevated due to a smaller mast cell burden in these six individuals.

Tryptase is measured by radioimmunoassay and serum is required. An important advantage of measuring serum tryptase is that determinations do not need to be made immediately after mast cell activation. Levels are maximal one to two hours following activation, and they usually remain elevated for several hours (248). Initially, this assay was not commercially available but now several laboratories provide this service. Tryptase determinations are available at Parkland Memorial Hospital, Zale-Lipshy University Hospital and the Aston Center.

While the finding of elevated mast cell mediators is suggestive of the diagnosis it is not diagnostic. In the absence of skin lesions a bone marrow biopsy should be performed in order to establish the diagnosis as well as to determine the disease category. In patients with cutaneous manifestations and peripheral blood abnormalities, hepatomegaly, splenomegaly, or lymphadenopathy a bone marrow biopsy should be performed as well to determine the existence of an associated hematologic disorder. Additional evaluation, including bone scan, skeletal surveys, and GI studies should be performed in those individuals presenting with bone or GI symptoms, respectively. Since decreased attention span, memory impairment and irritability have been noted in some individuals with mastocytosis (203) a neuropsychiatric evaluation may be warranted. In 1991 participants of a roundtable discussion on mastocytosis developed a consensus diagnostic workup which is presented in Figure 23.

Figure 23

CONSENSUS DIAGNOSTIC WORK-UP*

If mastocytosis is suspected on clinical grounds:

Routine

Examine skin - gross/microscopic
Bone marrow biopsy and aspiration
24-hour urine for mediators

Additional studies

Bone scan/skeletal survey
GI work-up
EEG, neuropsychiatric work-up

*From Metcalfe, Conclusions. J Invest Dermatol 96(suppl):64S, 1991 (Ref 169).

Treatment

The chronic treatment of mastocytosis should be aimed at blocking the effects of the released mast cell mediators as well as stabilizing the mast cell itself. Mediator release leads to the prominent manifestations of anaphylaxis, gastric hypersecretion, GI cramping and pruritus (203).

H_1-and H_2-receptor antagonists - H_1-receptor antagonists, such as hydroxyzine and the tricyclic antidepressant, doxepin, remain mainstays of treatment and have been shown to reduce pruritus, flushing and tachycardia (203). While the new long-acting, nonsedating H_1-antihistamines may prove to be beneficial, to date, no controlled studies have been performed. Patients with gastritis and peptic ulcer disease have been shown to be controlled with H_2-antihistamines. However, in patients with diarrhea H_2-antihistamines are usually not effective (249) and, in these individuals anticholinergics may be beneficial. Often, both H_1- and H_2-receptor antagonists are required to completely block the effects of histamine (250,251). However, despite this combination some patients continue to complain of flushing and headaches. In these individuals the levels of histamine may be very high or, more likely, the symptoms are secondary to other mast cell mediators that are unaffected by antihistamines.

Aspirin - In many patients PGD_2, as well as histamine, is elevated and, as expected, the episodes of vasodilation in these individuals are not controlled with antihistamines alone (252). While aspirin has been shown to be effective in these patients, high salicylate levels are necessary to achieve control (253). In light of the potential mast cell activating effects of aspirin, initial treatment should consist of combined antihistamine therapy. Subsequently, if no benefit is achieved, aspirin may be judiciously added and increased gradually until plasma salicylate levels rise to 20-30 mg/dl (254). If a patient does not respond to aspirin therapy he or she can not be considered a treatment failure unless effective cyclooxygenase inhibition has been ensured either by documentation of high salicylate levels or decreased production of urinary PGD_2 metabolites. Other nonsteroidal anti-inflammatory drugs have not been used extensively since blood levels of these agents can not be monitored. Unfortunately, many mastocytosis patients have GI symptomatology and often, these individuals are unable to tolerate aspirin.

Mast cell stabilizing agents - Cromolyn sodium, a stabilizer of mast cell membranes, has been found to be somewhat efficacious in mastocytosis patients, especially those with GI symptoms (189,190,253). While only 1% of orally administered cromolyn sodium is absorbed from the GI tract, it has been shown to alleviate both diarrhea and abdominal pain in patients with these symptoms (190). In addition, pruritus, whealing, flushing, and cognitive function have been shown to improve. Interestingly, despite clinical improvement, mastocytosis patients do not demonstrate decreased urine and plasma histamine levels while on treatment with this agent (189). Another treatment choice is ketotifen, an H_1-receptor antagonist with mast cell stabilizing

properties. While demonstrating effectiveness in relieving pruritus and wheeling associated with mastocytosis, a double-blind, placebo-controlled crossover study of eight children revealed this drug to be no more effective than hydroxyzine in relieving the symptoms of mastocytosis (256).

Psoralens with long-wave ultraviolet irradiation (PUVA) - Mastocytosis patients with urticaria pigmentosa have been shown to have decreased wheeling and pruritus after one to two months of treatment with PUVA (196-199). However, unfortunately, within months of ceasing therapy symptoms often recur. In light of the potential side effects of long-term PUVA therapy, this treatment is recommended only for those individuals with cutaneous disease unresponsive to other forms of therapy.

Steroids - In cases of severe malabsorption, which results from mast cell infiltration of the lamina propria of the small intestine, oral corticosteroids have led to marked improvement (230). Steroids have also been shown to be effective in reducing the ascites that may occur in the presence of liver fibrosis (257). Unfortunately, steroids may exacerbate the bone disease often present in patients with SMCD and, for that reason, they should be reserved for patients with severe malabsorption. More recently, tixocortol pivalate, a steroid without significant adrenal-pituitary axis suppression, was shown to alleviate both diarrhea and abdominal pain four patients (258).

Chemotherapy - Chemotherapy is not indicated in the treatment of type I mastocytosis. However, for patients with type II disease, therapy is dictated by the associated hematologic disorder. Chemotherapy has not been shown to be effective in the treatment of mast cell leukemia.

Splenectomy - Recently, the records of 26 patients with mastocytosis were reviewed to determine the role of splenectomy in the management of SMCD (259). Seventeen (65%) patients with indolent disease (type I mastocytosis) did not undergo splenectomy; symptomatic treatment only was required. Nine (35%) had type II or type IV disease, and five of these underwent splenectomy. The patients who did not undergo splenectomy died from bleeding complications caused by severe thrombocytopenia. Length of survival was in these patients was 26 months, whereas it was 34 months at the time of the report for those who had undergone splenectomy. These data suggest that, while splenectomy is of no value in patients with indolent mastocytosis, it may be beneficial in those with aggressive disease.

Additional considerations - If mastocytosis patients are to undergo surgery several precautions should be taken. Muscle relaxants that are known to degranulate mast cells should be avoided as should succinyl choline and opiates. In addition, it has been suggested that these patients be premedicated with H_1- and H_2-antihistamines prior to the procedure (253). Radiocontrast dye, too, must be administered with caution. Patients should be premedicated with antihistamines and steroids and the less, hyperosmolar agents should be used. Patients who experience recurrent episodes of

anaphylaxis should be treated with H_1- and H_2-antihistamines chronically and they should carry a premeasured epinephrine preparation at all times. Rarely, anaphylaxis following a Hymenoptera sting has been seen as the presenting symptom of systemic mastocytosis and interestingly, many of the patients that have been studied did not have antigen-specific IgE (188, 260). These patients too should be encouraged to carry epinephrine at all times.

Figure 24

Treatment of Mastocytosis*

Antihistamines:

H-1 receptor blockade
H-2 receptor blockade

Epinephrine
Steroids
Cromolyn sodium
Aspirin
Anticholinergics
PUVA
Chemotherapy
Splenectomy

*From Metcalfe, The Treatment of Mastocytosis. J Invest Dermatol 96(suppl):55S, 1991 (Ref 253).

Experimental Interventions

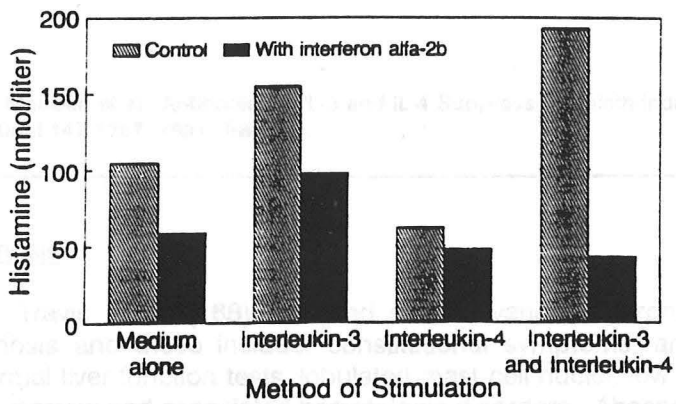
While antiproliferative drugs and radiotherapy have not been effective in the treatment of mastocytosis (168) alternative agents may be beneficial in the treatment of certain types of mastocytosis. Kluin-Nelemans et al. (261) demonstrated improvement in a male patient with aggressive mastocytosis and an associated myeloproliferative disorder (category II) after treatment with interferon alfa-2b. Prior to therapy, the patient's bone marrow contained a large percentage of atypical mast cells, fibrosis, and almost no residual hematopoiesis. After seven months of therapy the percentage of mast cells had decreased dramatically and hematopoietic cellularity significantly improved as well. Clinical improvement was noted after two months of therapy. Red cell transfusion

requirements were reduced in frequency, as were attacks of flushing, generalized itching, abdominal pain, vomiting, diarrhea, hypotension and syncope. After 12 months the patient's urticarial pigmentosa lesions had almost resolved; the liver was no longer palpable and his ascites was gone.

Over the course of therapy the urinary excretion of N-methylhistamine and N-methylimidazoleacetic acid rapidly decreased. In order to determine if the reduction in the urinary excretion of histamine metabolites resulted from decreased release of histamine from mast cells, *in vitro* experiments were performed using bone marrow mast cells obtained prior to therapy with interferon alfa-2b. As shown in Figure 26, bone marrow mast cells spontaneously released histamine when cultured in media alone. This secretion was enhanced by interleukin-3 alone and by interleukin-3 and interleukin-4 together, but not by interleukin-4 alone. When interferon alfa-2b was added to the cultures, both the spontaneous and the induced release of histamine was reduced markedly. Cell viability was not affected. These results, taken together, suggest that interferon alfa-2b has both an antisecretory and an antiproliferative effect on malignant mast cells and that it may be effective in some forms of aggressive mastocytosis.

Figure 25

EFFECT OF ALFA-2B ON *IN VITRO* SECRETION OF HISTAMINE BY BONE MARROW MAST CELLS*



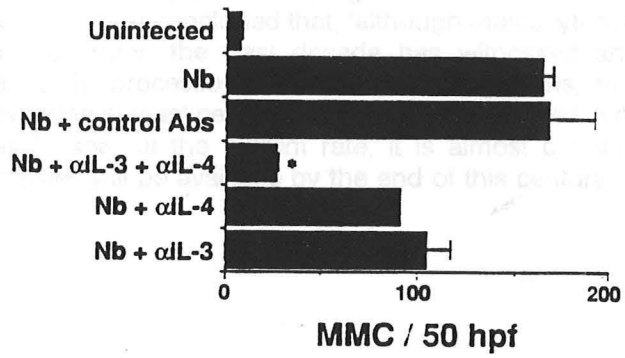
*From Kluin-Nelemans et al., Response to Interferon Alfa-2b in a Patient with Systemic Mastocytosis. N Engl J Med 326:619, 1992 (Ref 261).

Experimental results in rodents suggest that cytokine manipulation may be useful in treating mastocytosis. Infection in rodents with the nematode parasite *Nippostrongylus brasiliensis* (Nb) leads to intestinal mastocytosis, eosinophilia, and

elevated serum IgE levels. Madden et al. (262) demonstrated that by injecting young Balb/c mice with monoclonal antibodies to IL-3 and IL-4 prior to Nb infection, intestinal mastocytosis does not develop. These results demonstrate that IL-3 and IL-4 are important *in vivo* in the generation of intestinal mastocytosis and that therapeutic interventions designed to inhibit these cytokines may lead to suppression of disease.

Figure 26

SUPPRESSION OF INTESTINAL MASTOCYTOSIS BY ANTI-IL-3 AND ANTI-IL-4*



*From Madden et al., Antibodies to IL-3 and IL-4 Suppress Helminth-Induced Intestinal Mastocytosis. J Immunol 147:1387, 1991 (Ref 262).

Prognosis

Travis et al. (168) identified several variables strongly associated with poor prognosis and these include: constitutional symptoms, anemia, thrombocytopenia, abnormal liver function tests, lobulated mast cell nuclei, low percentage fat cells in the bone marrow and associated hematologic disorders. Absence of urticaria pigmentosa, male sex, hepatomegaly, splenomegaly, normal bone radiographic findings and absence of skin and bone symptoms also are associated with poor prognosis. In addition to these variables, prognosis is dependent upon the category of disease. Patients in category I who have cutaneous involvement only have the best prognosis. While approximately half of children with isolated urticaria pigmentosa are lesion-free by adulthood, adults who present with urticaria pigmentosa often develop systemic disease. The course for patients with an associated hematologic disorder is dependent upon the

adulthood, adults who present with urticaria pigmentosa often develop systemic disease. The course for patients with an associated hematologic disorder is dependent upon the prognosis of the particular hematologic disorder itself. Survival for patients with mast cell leukemia is usually less than six months, while individuals with lymphadenopathic mastocytosis with eosinophilia survive two to four years with aggressive symptomatic management (203).

Conclusion

Mastocytosis is, as was stated by Tharp (156) ten years ago, a "spectrum of disorders" in which aberrant mast cell proliferation is heterogeneous in its predilection for particular organs. More recently, at the closing of a roundtable discussion on mastocytosis in 1991, Metcalfe (169) concluded that, "although mastocytosis remains in some ways an enigmatic disorder, the past decade has witnessed an increased awareness of its significance, the processes involved in its pathogenesis, and advances in its therapy." If our knowledge of mast cells and the cytokines involved in their growth and regulation continues to soar at the current rate, it is almost certain that more effective therapeutic modalities will be available by the end of this century.

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