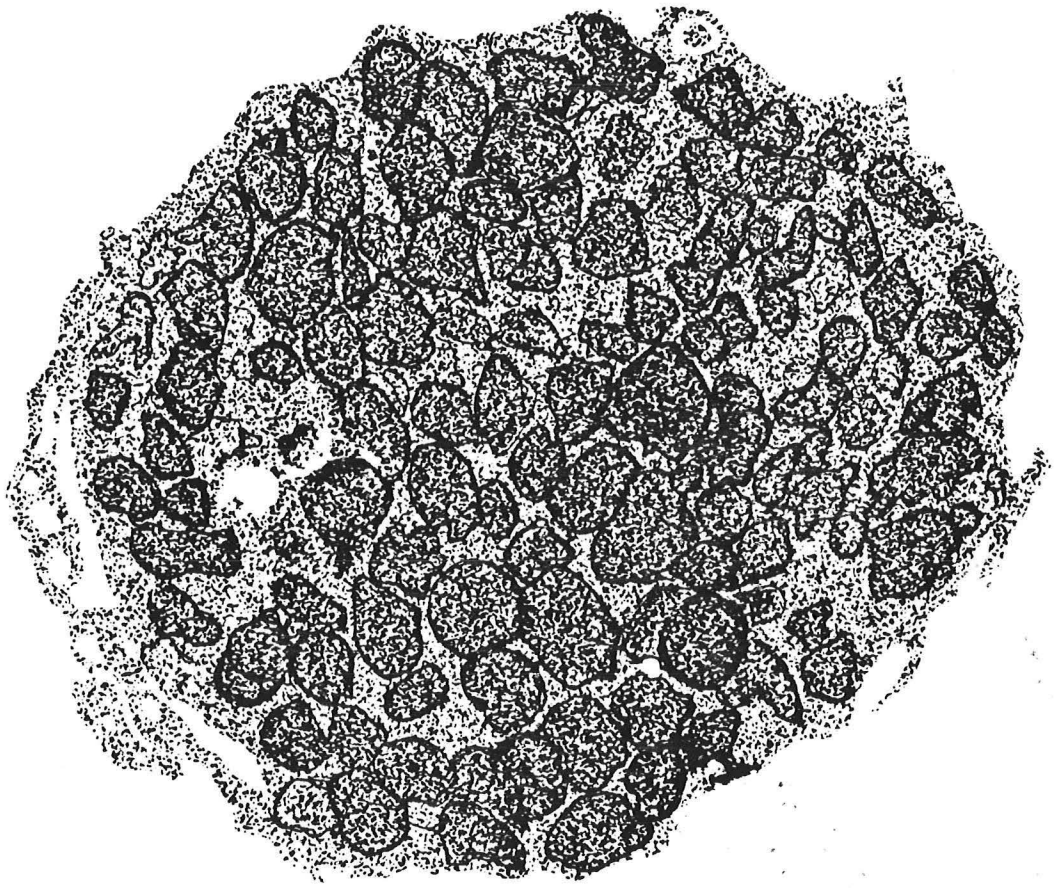
allergy

Medical Grand Rounds

July 19, 1984

THE SPECTRUM OF MASTOCYTOSIS



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Introduction

Mastocytosis is a spectrum of clinical disorders that results from an abnormal proliferation of tissue mast cells. Nettleship and Tay (1869) are credited with the original description of this disease in their report of a 2 year old girl with persistent, hyperpigmented cutaneous lesions that spontaneously urticated. However, it was not until eight years later that Paul Ehrlich (1877) formally identified the tissue mast cell. In his thesis, Ehrlich described a granule-laden connective tissue cell that he proposed had phagocytic properties; hence the name mast cell (MASTZELLEN), derived from the German term "Mastung", to masticate or to chew. Nine years after Nettleship and Tay's original report, Sangster (1878) described a patient with an "anomalous mottled rash accompanied by pruritus, urticaria and pigmentation". He termed this cutaneous eruption, Urticaria Pigmentosa. The etiology of these unusual appearing skin lesions remained unknown until Unna (1887) demonstrated dense accumulations of dermal mast cells in skin specimens from patients with this disorder. Touraine and coworkers (1933) proposed that this disease might also involve internal organs, and Ellis (1949) formally proved their hypothesis with the first reported autopsy findings in a 1 year old girl with mastocytosis. In this patient, mast cell infiltrates were observed in the skin, liver, spleen, lymph nodes, and bone marrow. Thus, within a span of eighty years, the concept of mastocytosis had evolved from one of a mere cutaneous affliction to that of a systemic, and potentially fatal, disorder.

Today mastocytosis is recognized as a group of clinical disorders, some of which result from mast cell infiltrates localized to the skin while others clearly represent a systemic, proliferative mast cell process. Because of the varied clinical presentations within the mastocytosis spectrum, a number of descriptive terms have evolved (Table I). Over the years this nomenclature has become not only cumbersome, but also confusing, sometimes resulting in the incorrect use of specific terminology. Thus, for simplification, the general term MASTOCYTOSIS is used in this discussion and includes all of the recognized mast cell proliferative disorders. The disorders within the mastocytosis spectrum can be categorized into one of two groups: those in which the disease is localized to the skin (Cutaneous Mastocytosis) and those which are associated with multi-organ mast cell infiltrates (Systemic Mastocytosis). Using this simple classification, the important clinical features of the disorders within each group will be reviewed and a rational approach to diagnosis and treatment will be outlined.

In order to better understand the pathophysiology underlying the varying clinical presentations of mastocytosis, an overview of normal tissue mast cell morphology and function is presented.

Table I

DESCRIPTIVE TERMS FOR CLINICAL DISORDERS

WITHIN THE MASTOCYTOSIS SPECTRUM

Chromelasma Urticans

Disseminated Mastocytoma

Mast Cell Reticulosis

Nettleship's Disease

Nevus Pigmentosus Urticans

Papular Erythema

Permanent Erythema

Pseudo-Xanthoma Urticans

Solitary Mast Cell Nevus

Telangiectasia Macularis Eruptiva Perstans

Urticaria Neviformis

Urticaria Perstans Hemorrhagica

Urticaria Perstans Pigmentosa

Urticaria Pigmentosa

Xanthelasmoidea

Xanthomoieda Urticans

Sagher and Even-Paz, 1967

THE TISSUE MAST CELL

Distribution and Morphology

Human tissue mast cells are normally distributed widely throughout the body with a relative predilection for host-environment interfaces (i.e. the skin, upper and lower respiratory tract and the gastrointestinal tract). In addition, the thymus, uterus, and urinary bladder have a significant mast cell population. Conversely, relatively few mature mast cells reside within normal human liver, spleen, bone marrow or lymph nodes. In most tissues mast cells are generally concentrated around small blood vessels, lymphatics, nerves and glandular tissue. (Asboe-Hansen, 1954; Sagher and Even-Paz 1967, Eady, 1976). In human skin, mast cells are observed around hair follicles, sebaceous glands and sweat glands. Approximately 7000 to 10,000 cutaneous cells are normally present per cubic millimeter of tissue. (Eady, 1976; Metcalfe et al., 1980)

Human tissue mast cell morphology may range from ovoid to spindle-shaped to a "tadpole-like" configuration. Work in our laboratory examining whole mounts of human dermis indicate that mast cells are often dendritic which may account, in part, for the apparent pleomorphism noted in routine, vertical histological sections (Bergstresser et al. 1984). Human mast cells vary in size from 10 to 15μ in diameter. The cell nucleus is usually round or oval in shape, and can be readily differentiated from the lobulated nucleus of the circulating basophil. The mast cell double-layered plasma membrane appears relatively uniform under light microscopy; however, studies using transmission electron microscopy (EM) clearly demonstrate the villous or "ruffled-appearing" nature of this membrane barrier (Fig. 1A). Tissue mast cells have the expected normal complement of cellular organelles including ribosomes, endoplasmic reticulum, mitochondria, Golgi's apparatus and microfilaments. The characteristic feature of the mast cell, however, is the presence of cytoplasmic granules that are so numerous that they often obscure the nucleus. Mast cell granules range in size from 0.2 to 0.5μ in diameter, and appear to be limited by a bilayered membrane (Hashimoto et al., 1966; Orr, 1977). Transmission electron microscopic studies demonstrate a dense or amorphous material in rodent mast cell granules while similar studies in human tissue mast cells frequently show a scroll or lattice-like granule morphology (Fig. 1B). These apparent structural differences between rodent and human mast cells are not understood.

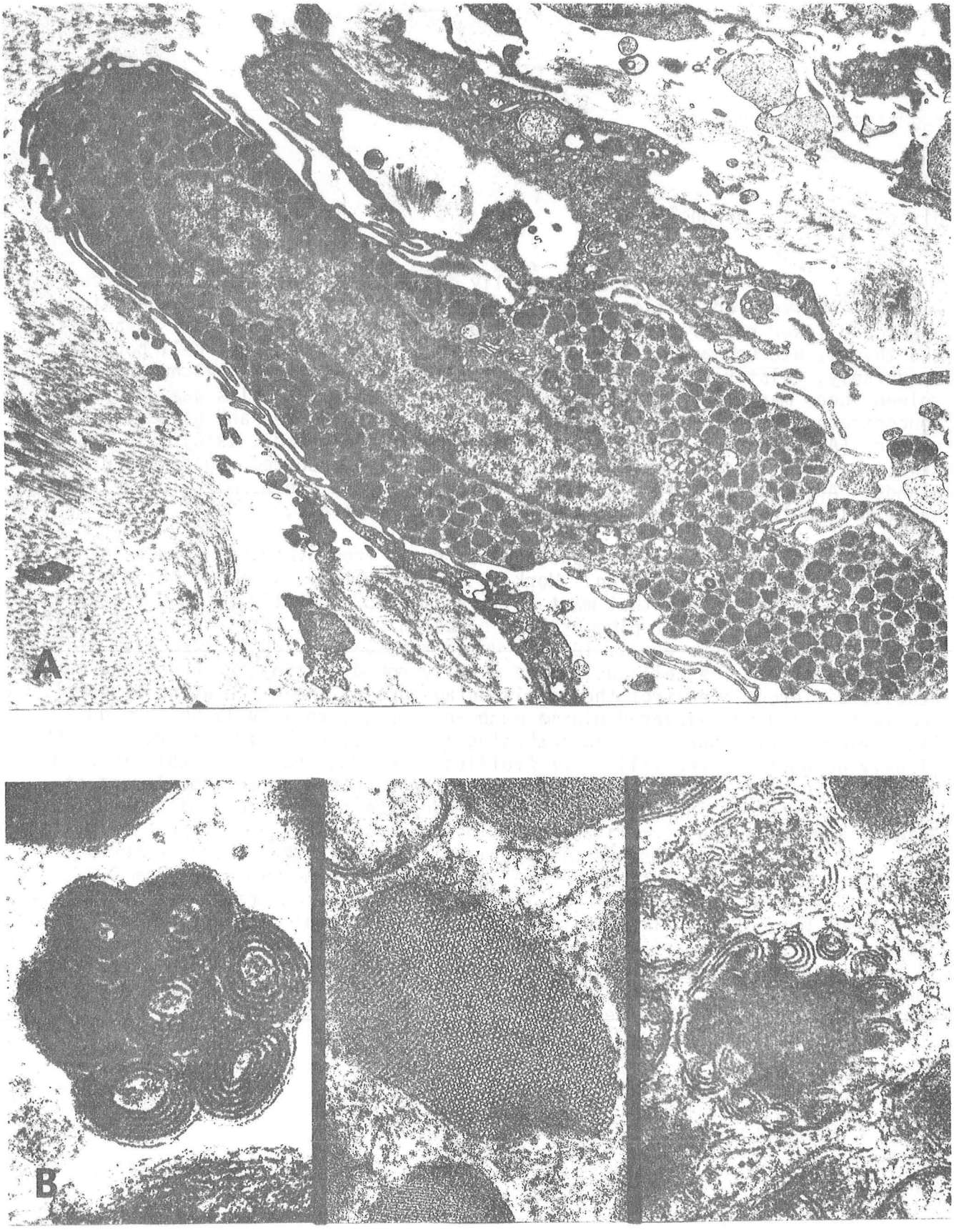


Fig. 1. Transmission EM of a human cutaneous mast cell (A). Varying morphology of internal structures within human mast cell granules (B).

Staining Characteristics

A variety of metachromatic dyes including toluidine blue, giemsa, methylene blue, azure A, and methyl green have been employed for specifically identifying mast cells in histological sections (Devitt et al., 1954; Montagna and Melaragno, 1953; Kramer and Windrum, 1955). The mechanism underlying metachromatic staining involves the stacking of cationic dye molecules onto the dense, negatively charged heparin polymer, resulting in a shift in light absorbance. (Kramer and Windrum, 1955). Although the metachromatic stains classically have been employed for identifying mast cells in tissues, they have proven to be difficult for routine use. Some dyes require special fixatives while others are highly dependent upon the time of tissue fixation. In addition, most metachromatic staining methods are altered by small changes in dye pH. Non-metachromatic stains for mast cell identification also have been developed. The chloroacetate esterase stain selectively demonstrates mast cells and neutrophils in tissue sections, and depends upon cleavage of the ester linkage by mast cell granule-associated proteolytic enzymes (Benditt and Lagunoff, 1964). This histochemical method, however, has the disadvantage of staining both mast cells and neutrophils. More recently, we have developed and characterized a technique using conjugated-avidin preparations that is highly sensitive for identifying mast cells in tissues. (Bergstresser et al. 1984; Tharp et al. 1984). Avidin conjugated to the fluorochrome dyes, (fluorescein isothiocyanate or tetramethylrhodamine isothiocyanate) or to horseradish peroxidase binds specifically to mast cells in tissues. Unlike the metachromatic and esterase stains, the conjugated avidin staining technique does not stain neutrophils nor is it limited by methods of fixation, small changes in pH, or special cutting and embedding procedures. This technique already has proven to be a simple and reliable method for identifying and enumerating mast cells in tissues.

Mast Cell Origin

Although the mast cell was formally identified over 100 years ago, its origin(s) still remains controversial. Putative mast cell precursors have included primitive mesenchymal cells, fibroblasts, lymphocytes and thymocytes. (Fawcett, 1955; Johnstone, 1956; Csaba, 1960). In rodents, some mast cells arise from bone marrow precursors. Studies by Kitamura and coworkers (1978) have demonstrated that mice deficient in mast cells (W/W^{v}) develop a normal tissue mast cell population three to four months after bone marrow transplantation. Further evidence for a bone marrow-derived mast cell precursor also can be extrapolated from observations made in the Beige mouse strain in which both circulating granulocytes and tissue mast cells have large, atypical cytoplasmic granules. A similar observation has been made in the granulocyte and mast cell populations of patients with the Chediak-Higashi Syndrome. Bone marrow origin of human mast cells also is suggested by reports of increased tissue mast cells in some bone marrow specimens from patients with hematologic disorders (polycythema rubra vera, myelofibrosis, and acute and chronic leukemias) (Bowdler and Tullett, 1960; Diamond and Gross, 1966; Udoji and Razavi, 1975; Lennert and Parwaresch, 1979; Parkin et al., 1980). In addition, there are obvious similarities between the tissue mast cell and the circulating,

bone marrow-derived basophil. Both cell types have metachromatic granules, intracellular histamine stores, eosinophil chemotactic factors, and surface-bound IgE molecules. Recently, Zucker-Franklin (1980) described an "intermediate cell" in patients with myeloproliferative disorders with ultrastructural properties of both tissue mast cells and circulating basophils, suggesting a common stem-cell precursor. Finally, increased numbers of mast cells are commonly observed in bone marrow specimens from patients with systemic mastocytosis (Sagher and Even-Paz, 1967; Friedman et al., 1958; Klatt et al., 1983). Taken together, these observations provide strong, indirect evidence of a bone marrow-origin for human tissue mast cells.

Mast Cell Subpopulations

Recent studies in rodents have suggested that at least two distinct populations of mast cells may exist, Connective Tissue Mast Cells (CTMC) and Mucosal Mast Cells (MMC). (Befus et al., 1982). The distinguishing characteristics of CTMC and MMC are detailed in Table II. Representatives of the CTMC subset are mast cells found in the skin and peritoneal cavity of rodents while cells with the characteristics of MMC have been identified in the gastrointestinal tract and bone marrow. To date similar subpopulations of tissue mast cells have not been clearly defined in man although preliminary studies suggest that human intestinal mast cells may differ functionally from human pulmonary mast cells. At present it is unclear if this apparent heterogeneity observed among rodent mast cells reflects differences in cellular origin or represents a variation in the degree of cell differentiation. It is conceivable, however, that mast cells arise from a single type of precursor in the bone marrow, spread to tissues via the circulation, and proliferate and/or differentiate at various anatomical sites according to controls imposed by local regulatory forces. Transmission EM studies in rodents support such a hypothesis. Immature mast cells arising in the connective tissue (CTMC) of rodent embryos appear very similar ultrastructurally to mast cells cultured *in vitro* from murine bone marrow (MMC) (Combs, 1971). To date, the forces that promote and govern tissue mast cell growth are poorly understood. However, a growth promoting factor that is elaborated from lymphocytes, Interleukin 3, has been identified and appears critical for the *in vitro* development of MMC (Ihle et al., 1983). Our future understanding of IL-3 and other forces that regulate mast cell growth and development may provide insight into the apparent differences of these mast cell subpopulations.

Table II

REPORTED DIFFERENCES IN RODENT MAST CELL POPULATIONS

Properties	Mucosal Mast Cell (MMC)	Connective Tissue Mast Cells (CTMC)
Morphology	Fewer granules	Many granules
Size	9.7μ	19.6μ
Thymus-dependent proliferation	Yes	No
Serine Protease	Type II	Type I
Proleoglycan	Non-Heparin	Heparin
Histamine Content	1.3pg/cell	15pg/cell
Lifespan	<40 days	>6 mos.
Response to 48/80	Resistant	Susceptible

Mast Cell Secretagogues

Degranulation of tissue mast cells results from both immune and non immune-mediated mechanisms (Table III). Perhaps the most clinically relevant of these mechanisms involves the interaction of antigens and IgE molecules bound to receptors on the mast cell surface. The cross-linking of these surface immunoglobulins by specific multivalent antigens provokes mast cell degranulation that appears clinically as an immediate hypersensitivity reaction. The IgE molecule is composed of two light and two heavy chains linked covalently by disulfide bonds, and has a molecular weight of approximately 190,000 daltons (Ishizaka et al., 1970; Bennich and Johansson, 1971). The number of mast cell surface receptors for IgE ranges from 100,000 to 500,000 with approximately 10 percent of the receptors being occupied by IgE under normal conditions. However, in patients with high levels of serum IgE (∿1000ng/ml), circulating basophils, and presumably tissue mast cells, have up to 95% of their receptors occupied by this immunoglobulin (Malveaux et al., 1978). Unlike the rodent, human tissue mast cells do not have receptors for IgG molecules, and thus, circulating IgG does not serve as a mast cell-secretory agonist. A second immune mechanism for mast cell stimulation involves the generation of the complement anaphylatoxins, C_{3a}, C_{4a}, and C_{5a}. These low molecular weight peptides appear to stimulate mast cells through distinct receptors, and are active human mast cell secretagogues both *in vivo* (Lepow et al., 1970) and *in vitro* (unpublished observations, Tharp and Sullivan). The anaphylatoxins have a

rank order of potency in which $C_{5a} > C_{3a} \geq C_{4a}$ with C_{5a} being approximately 100-fold more potent than C_{3a}. (Hartman and Glovsky, 1981).

A number of other naturally occurring and exogenous nonimmune agents also appear capable of stimulating mast cell mediator release (Table III). The adenine nucleotides, ATP and ADP, have been demonstrated to be potent human mast cell secretagogues both in vitro and in vivo (Tharp et al., 1981; Coutts et al., 1981). These molecules have potential clinical relevance since there are several known sources of extracellular ATP and ADP in close proximity to tissue mast cells (cholinergic and adrenergic nerve endings, endothelial cells, secretory tissues, such as the adrenal gland, and platelets). Several naturally occurring hormones such as ACTH (Asboe-Hansen, 1950) and estrogens (Schiff and Burn, 1961) also have been implicated in modulating tissue mast cell response. Recently, we have demonstrated that the hormone gastrin and its active pentapeptide pentagastrin, (but not its N-terminal tridecapeptide) can provoke human cutaneous mast cell mediator release. (Tharp et al., 1984). This observation may have clinical relevance in light of the reported postprandial immediate hypersensitivity-like reactions that are associated with eating but are neither food-specific nor IgE-mediated. (Kidd et al., 1983; Novey et al., 1983). Gastrin's effects on mast cells may play a role in the pathogenesis of duodenal ulcers, diarrhea and/or malabsorption syndromes seen in some patients with mastocytosis. (Belcon et al., 1980 and Broitman et al., 1970).

Table III

CLINICALLY RELEVANT HUMAN

MAST CELL SECRETAGOGUES

Immunologic mechanisms

IgE-mediated

Anaphylatoxins (C_{3a}, C_{4a} & C_{5a})

Lymphokines

Non Immunologic mechanisms

Medications (Narcotics, Curare, Succinylcholine, Aspirin, Nonsteroidal anti-inflammatory agents, Polymyxin B)

Adenine Nucleotides (ATP, ADP)

Hormones (Gastrin, ACTH, Estrogens)

Radiocontrast media

Complex carbohydrates

Venoms

Irradiation

Biochemistry of Mast Cell Secretion

There are a number of biochemical events that occur following mast cell stimulation which are associated with the release of preformed and newly-generated mediators. Changes in cyclic 3',5'-adenosine monophosphate (cAMP) levels, increased intracellular ionized calcium concentrations, phospholipid methylation, membrane phospholipid turnover, arachidonic acid metabolism, and intracellular protein phosphorylation have been documented in either rodent or human mast cell models following stimulation. Studies in rat and human mast cells indicate that a rise in cAMP occurs within 15 seconds after an IgE-mediated signal, and then falls to near baseline values at the time of histamine release (Sullivan et al., 1975; Ishizaka et al., 1983) (Fig. 2). Several investigators also have identified a second rise in cAMP that occurs after peak histamine release which is suppressed by cyclooxygenase inhibitors, thereby possibly affecting arachidonic acid metabolism and prostaglandin formation. It is thought that the generation of prostaglandin D_2 (PGD_2) might be responsible for this second peak in cAMP activity. Contrary to the popular theory that all rises in cAMP levels result in the inhibition of mast cell mediator release, increases in cAMP induced by PGD_2 fails to inhibit rat mast cell secretion (Holgate et al., 1980). This apparent contradiction may be best explained in terms of cAMP activation of protein kinases which may modulate the mast cell secretory process. Subsequent to cAMP generation, these protein kinases are stimulated by IgE-mediated events but are not activated in the presence of PGD_2 (Holgate et al., 1981).

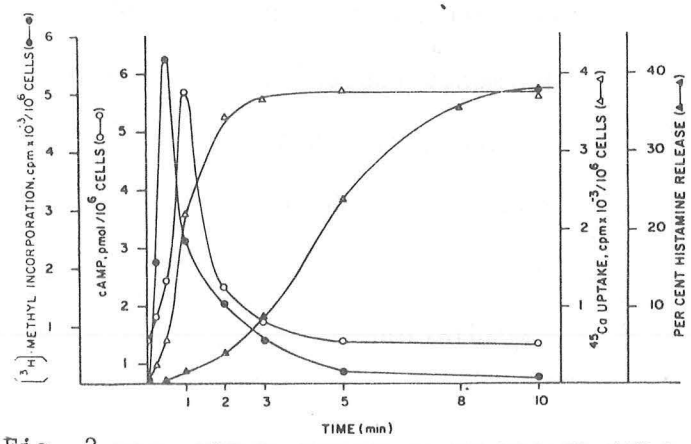


Fig. 2 Kinetics of [^{3}H]methyl incorporation into phospholipids (●), cAMP rise (○), ^{45}Ca uptake (△), and histamine release (▲) induced by anti-IgE. Mast cells were incubated overnight with E myeloma protein to saturate IgE receptors, then were challenged with 0.9 μg/ml of anti-IgE. The same mast cell preparation (purity of 90%) was employed in all measurements. Each point is an average of duplicated measurements. [^{3}H]methyl incorporation and ^{45}Ca uptake by unstimulated cells were 2010 cpm/10^6 and 1780 cpm/10^6, respectively. Spontaneous histamine release from the cells was 9%. These values were subtracted from experimental values. The original cAMP level in the unstimulated cells was 1.45 pmol/10^6 cells.

The importance of calcium in mast cell secretion is well-established. With the exception of the secretagogue, compound 48/80, mast cell agonists require the presence of extracellular calcium. Normally the intracellular calcium concentration of mast cells is less than 1/10,000 of that measured in the extracellular fluid. At the time of mast cell activation, it is believed that cellular calcium channels are created which facilitate the influx of this cation. Calcium appears to be an important cofactor for a number of intracellular events. Work in our laboratory indicates that both low and high concentrations of added calcium have apparent inhibitory effects on human mast cell secretion in vitro (Tharp et al., 1983).

Biochemical studies examining mast cell membrane phospholipid methylation indicate a marked increase in activity within 15 seconds of mast cell stimulation (Ishizaka et al., 1980 and 1983). In cells that methylate phospholipids, two methyltransferases are usually present with one facing the cytoplasmic side of the cell membrane and methylating phosphatidylethanolamine to phosphatidyl-N-monomethylethanolamine and the second facing the outer cellular membrane surface which actively converts phosphatidyl-N-monomethyl-ethanolamine to phosphatidylcholine. (Hirata and Axelrod, 1980) (Fig. 2). With an increase in methyltransferase activity, and hence an alteration in membrane phospholipids, a reduction in membrane viscosity is predictable. Conceivably these membrane changes may play a role in calcium channel formation. The intracellular accumulation of calcium could in turn augment phospholipase A_2 activity resulting in the hydrolysis of phosphatidycholine to arachidonic acid and lysophosphatidycholine. Lysophosphatidylcholine is a detergent-like fusogen, and has known mast cell stimulating capabilities (Poole et at., 1970). Studies by Kennerly et al., (1979a, 1979b) also have provided insight into potentially important membrane phospholipid changes that coincide with early phases of mast cell secretion. Within seconds after mast cell stimulation, phosphatidic acid, phosphatidylinositol, and phosphatidylcholine are generated. These phospholipid changes occur prior to and during the release process. Agents that modulate cAMP metabolism or inhibit arachidonic acid metabolism also decrease phospholipid turnover and mast cell mediator release (Marquardt et al., 1981). These parallel changes in phospholipid metabolism and mast cell secretion suggest an important role for the generation of certain membrane phospholipids in the mediator release process. In addition, a precursor of phosphatidic acid, diacylglycerol (DAG) has been demonstrated to rise two to four-fold in stimulated mast cells; a change that coincides with mast cell mediator release. DAG is also a known potent cell membrane fusogen making it another potentially important molecule for mast cell secretion.

At present, the relationships of these biochemical events during mast cell activation and secretion remains speculative. It is highly conceivable that some mast cell secretagogues provoke mediator release through different biochemical pathways. This is suggested by the observations in human basophils in which an IgE-mediated signal results in the release of histamine and leukotrienes while anaphylatoxin-induced activation produces only histamine release (Findlay et al., 1980). It is interesting to hypothesize that stimulation of the mast cell through its IgE receptors promotes phospholipid metabolism resulting in the liberation of arachidonic acid, formation of fusogenic substances, with subsequent alterations in membrane fluidity. These changes may in turn facilitate intracellular Ca^{++} ion movement. Concurrently,

stimulation of AC would be expected to activate cAMP-dependent protein kinases leading to the phosphorylation of key proteins (Fig. 3). These protein molecules may be critical in regulating the intracellular events that lead to mast cell degranulation.

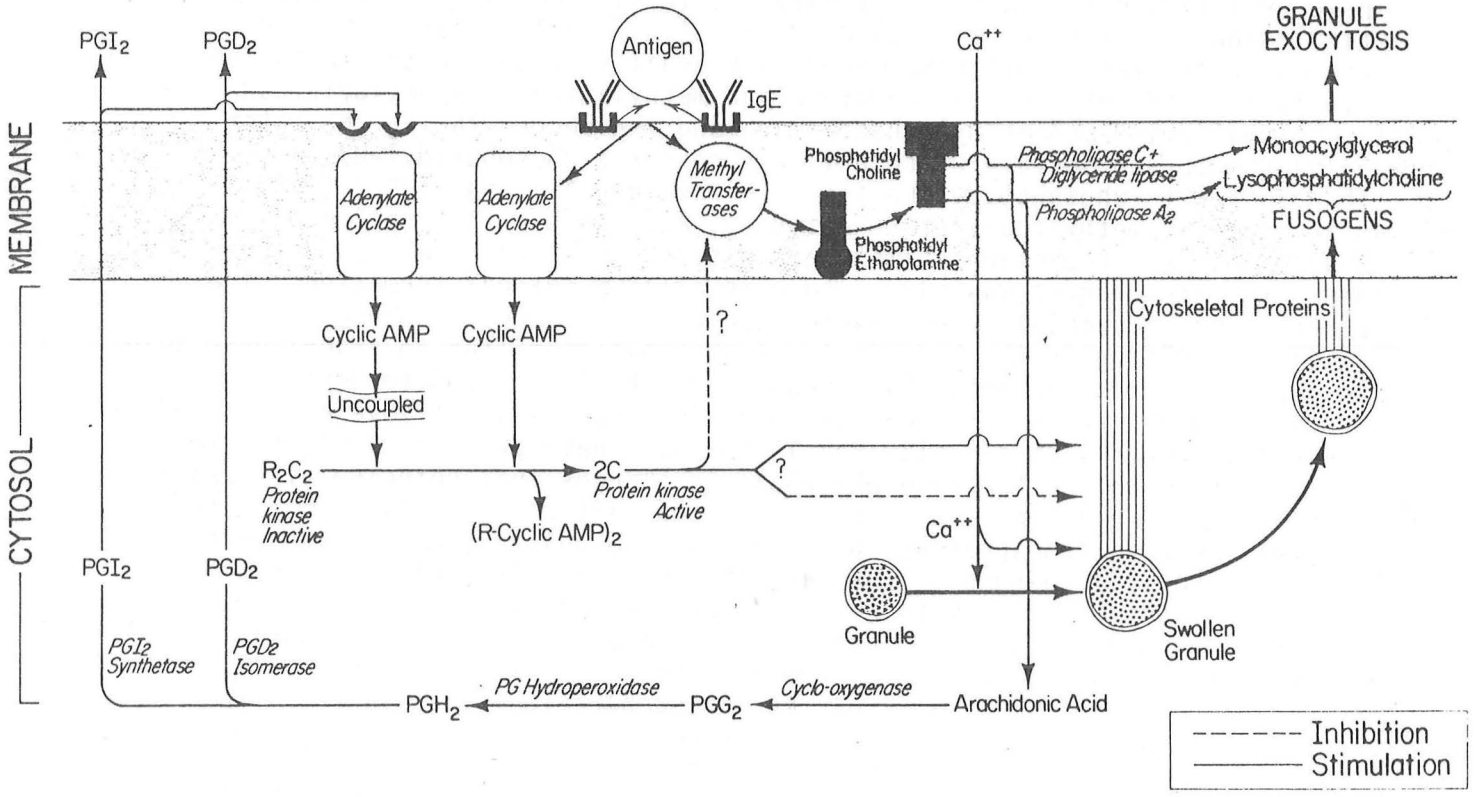


Figure 3. Biochemical events associated with IgE-mediated mast cell degranulation

Mast Cell Mediators

The mast cell generates a variety of pharmacologically potent molecules capable of modulating numerous physiologic and immunologic events. Two general categories of regulatory substances have been identified and consist of preformed, granule-associated mediators and newly-formed, unstored mediators that are generated at the time of mast cell activation (Tables IV and V). Observations in the rat mast cell indicate that preformed mediators such as histamine, are rapidly released at the time of mast cell stimulation. However, other preformed mediators (heparin, enzymes), which constitute a significant portion of the mast cell granule, appear to remain granule-bound after discharge from the cell. The newly-formed mediators (prostaglandins and leukotrienes), which are generated from arachidonic acid at the time of mast cell stimulation, are released from the mast cell within several minutes after an agonist signal. These observations indicate that a temporal effect of mast cell mediators may be operative, at least, in the local environment if not systemically.

The physiologic and pathologic consequences of mediator release are, in part, dependent upon the tissues in which they are secreted. For example, the clinical manifestation of histamine release in the skin and in the nose result from endothelial cell contraction and increased vasopermeability. While similar responses also occur in the lung, the most dramatic effect of histamine in this organ is smooth muscle contraction resulting in bronchoconstriction. Although immediate mast cell mediator discharge is responsible for the events associated with Type I allergic reactions (Immediate Hypersensitivity), the clinical effects of mast cell degranulation may persist for some time due to the temporal release of granule-bound mediators and due to the activation of other immune forces. In this section the preformed (Table IV) and newly-formed (Table V) mast cell mediators are discussed individually from both a physiologic and biochemical viewpoint.

HISTAMINE: The main source of tissue histamine is the mast cell, and under physiological conditions, its content in tissues corresponds closely to resident mast cell numbers. (Riley and West, 1953). Histamine formation results from the decarboxylation of L-histidine, and its degradation occurs through deamination with diamine oxidase (histaminase) or by methylation via histamine-N-methyl-transferase. Both of these histamine degrading enzymes are present in tissues while diamine oxidase is also present in circulating cells such as eosinophils and neutrophils (Zeiger et al., 1976; Zeiger and Colten, 1977). Histamine is excreted in the urine primarily in metabolized form with methylimidazoleacetic acid (MeIMAA) representing 60-80% of urinary histamine and the riboside of imidazoleacetic acid comprising 10-25% of this excreted amine. (Demis, 1982; Granerus, 1968) (Fig. 4).

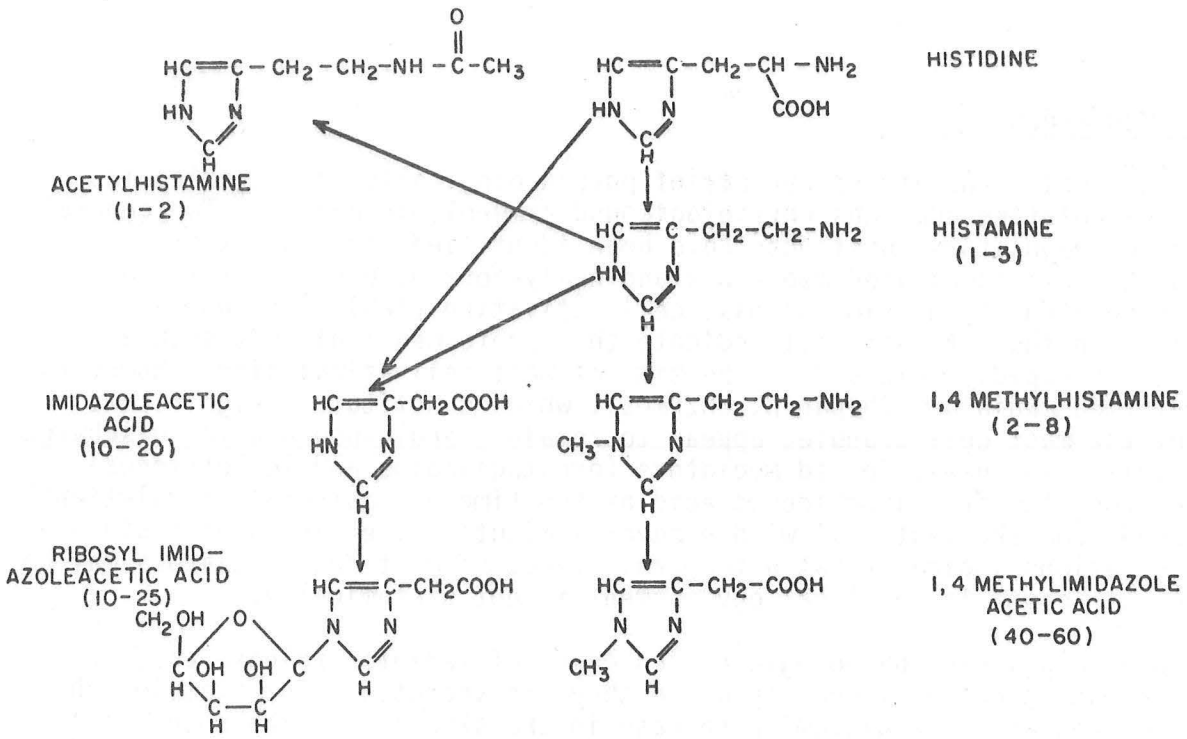


Fig. 4 Histamine metabolism. Histamine is formed (45, 46) by decarboxylation of histidine (histidine decarboxylase enzyme) and metabolized to specific metabolites—methylhistamine, methylimidazole acetic acid, and acetylhistamine. Imidazole acetic acid and its ribose conjugate are nonspecific metabolites. Numbers in parentheses refer to per cent of exogenous histamine excreted

The biologic effects of histamine release are mediated by two receptor subtypes, conventionally termed H_1 and H_2 receptors. Histamine$_1$ and histamine$_2$ receptors are present in a number of tissues and on circulating cells. Stimulation of H_1 receptors results in smooth muscle and endothelial cell contraction, prostaglandin production, and at micromolar concentrations, eosinophil chemotaxis (Table IV). Activation of H_2 receptors also increases vasopermeability through endothelial cell contraction, but in addition, augments gastric acid secretion, promotes mucous production, inhibits the release of histamine from basophils (but not human mast cells), inhibits lymphokine and neutrophilic-enzyme release, retards eosinophil migration, and reduces T-lymphocyte-mediated cytotoxicity, presumably through activation of suppressor T-lymphocytes (Rocklin, 1976; Rocklin, et al., 1979). In addition, histamine stimulation of the H_2 receptor augments cAMP levels in human leukocytes and pulmonary cells, while rises in cyclic GMP levels have been associated with activation of the H_1 receptor (Bourne et al., 1973; Platshon and Kaliner, 1978).

Because of its wide range of local and systemic effects, histamine is felt to play an important role in the clinical manifestations associated with mast cell degranulation. Indeed, the infusion of histamine in normal subjects provokes dose-related cutaneous flushing, pulsatile headaches, tachycardia, and hypotension which occur in association with plasma histamine levels ranging from

Table IV

Preformed Mast Cell Mediators

Mediator		Effect
*Histamine	H_1	Contracts smooth muscle Increases vasopermeability Increases cGMP Promotes prostaglandin synthesis Promotes eosinophil migration
	H_2	Increases vasopermeability Augments gastric acid secretion Increases mucous secretion Increases cAMP Stimulates suppressor T lymphocytes Inhibits basophil histamine release Inhibits lymphokine release Inhibits eosinophil migration
*Eosinophil Chemotatic factors of anaphylaxis (ECF-A)		Attracts eosinophils Increases eosinophil IgE receptors
*Neutrophil Chemotatic (NCF) factor		Attracts neutrophils
*Heparin		Anticoagulant Binds to antithrombin III and platelet factor IV Inhibits complement activation Binds other preformed mediators Promotes plasminogen activator release Promotes phospholipase A release Promotes triglyceride lipase release
Enzymes		Activates Hageman Factor bradykinin
* Tryptase		
Arylsulfatase A		Inactivates SRS-A
Hexosaminidase		Cleaves hexosamines
β Glucuronidase		Cleaves glucuronide residues
Superoxide dismutase		Cleaves oxygen radicals
Perioxidase		Cleaves H_2O_2

*Demonstrated in human mast cells.

1.6 to 2.5 ng/ml. Inhibition of these symptoms by pretreatment with antihistamines can be achieved; however, the use of both H_1 and H_2 receptor antagonists is necessary (Table V). These observations underscore the clinical relevance of released histamine in mast cell-mediated events, and emphasize the necessity of combined H_1 and H_2 antihistamines for effective therapy.

Table V Plasma levels of histamine required to elicit symptoms

Symptoms	Pretreatment			
	None (n = 12)	Cimetidine (n = 7)	Hydroxyzine (n = 7)	Cimetidine + hydroxyzine (n = 6)
	Plasma histamine levels (ng/ml)*			
Flush, headache	2.39 ± 0.52	3.10 ± 1.07	2.95 ± 0.19	5.76 ± 0.78 ($p < 0.001$)†
Increased heart rate (+30%)	1.61 ± 0.30	2.31 ± 0.35	4.15 ± 0.40 ($p < 0.001$)	6.07 ± 0.46 ($p < 0.0001$)
Widened pulse pressure (+30%)	2.45 ± 0.13	2.20 ± 0.26	1.63 ± 0.36	>6.07 ($p < 0.0001$)

n = number of patients studied.
*Data presented as mean ± SEM.
†Compared with baseline by paired sample t test.

CHEMOTACTIC FACTORS: A number of chemotactic factors are generated and released by the tissue mast cell, and include histamine, neutrophil chemotactic factors (NCF), and eosinophil chemotactic factors of anaphylaxis (ECF-A) (Table IV). At micromolar concentrations, histamine is selectively chemotactic for eosinophils while at higher concentrations it appears to inhibit eosinophil migration (Archer, 1956; Clark et al., 1975). A neutrophil chemotactic factor with a molecular weight of approximately 750,000 has been demonstrated in patients with cold-induced urticaria (Wasserman et al., 1977) and in individuals who are ragweed sensitive (Atkins et al., 1977). Two tetrapeptides (Ala-Gly-Ser-Glu and Val-Gly-Ser-Glu) that differ only in their N-terminal amino acid residue have been demonstrated to be potent chemotactic factors for eosinophils, hence the term eosinophilic chemotactic factors of anaphylaxis (ECF-A) (Goetzl and Austen, 1975). A larger, oligopeptide eosinophil chemotactic factor also has been reported in rat mast cells. Clinically, variable numbers of eosinophils are often observed in tissue sections from patients with urticaria and mastocytosis (Webb et al., 1982).

HEPARIN: The sulfated mucopolysaccharide heparin, with an approximate molecular weight of 60,000 daltons, has been identified in tissue mast cells from human skin and lung (Metcalfe et al., 1979; Metcalfe et al., 1980). Human heparin is comprised of a protein core to which glycosaminoglycan side chains are attached. By virtue of its high negative charge density, the heparin molecule appears to function as a storage matrix in the mast cell granule for histamine as well as for some chemotactic factors and enzymes. In addition to its anticoagulation effects, heparin may inhibit complement activation at several steps along the cascade. (Weiler et al., 1978) (Table IV). Despite these important physiologic influences, detectable abnormalities in coagulation and complement generation are rarely observed in patients with mastocytosis.

LYSOSOMAL ENZYMES: The human and rodent mast cell has a number of granule-associated enzymes including tryptase, arylsulfatase, β-hexosaminidase, β-glucuronidase, β-galactosidase, superoxide dismustase, and peroxidase (Table IV). These enzymes are not limited to the tissue mast cell; however, their release during mast cell-degranulation may have potentially important local and systemic effects. Tryptase, for example, may activate the Hageman factor and possibly cleave kininogen to facilitate bradykinin formation. The generation of kinins has been associated with pain, increased vascular permeability and smooth muscle contraction. Activation of the Hageman factor could potentially stimulate the clotting, fibrinolytic, and complement cascades. (Newball et al., 1975) Conversely, some mast cell enzymes appear to have potential anti-inflammatory effects. Arylsulfatase A has been reported to inactivate leukotrienes while superoxide dismutase, which facilitates the conversion of superoxide to hydrogen peroxide, may protect tissues from potentiallly toxic molecules. The overall in vivo relevance of these granule-associated enzymes following mast cell secretion remains to be demonstrated.

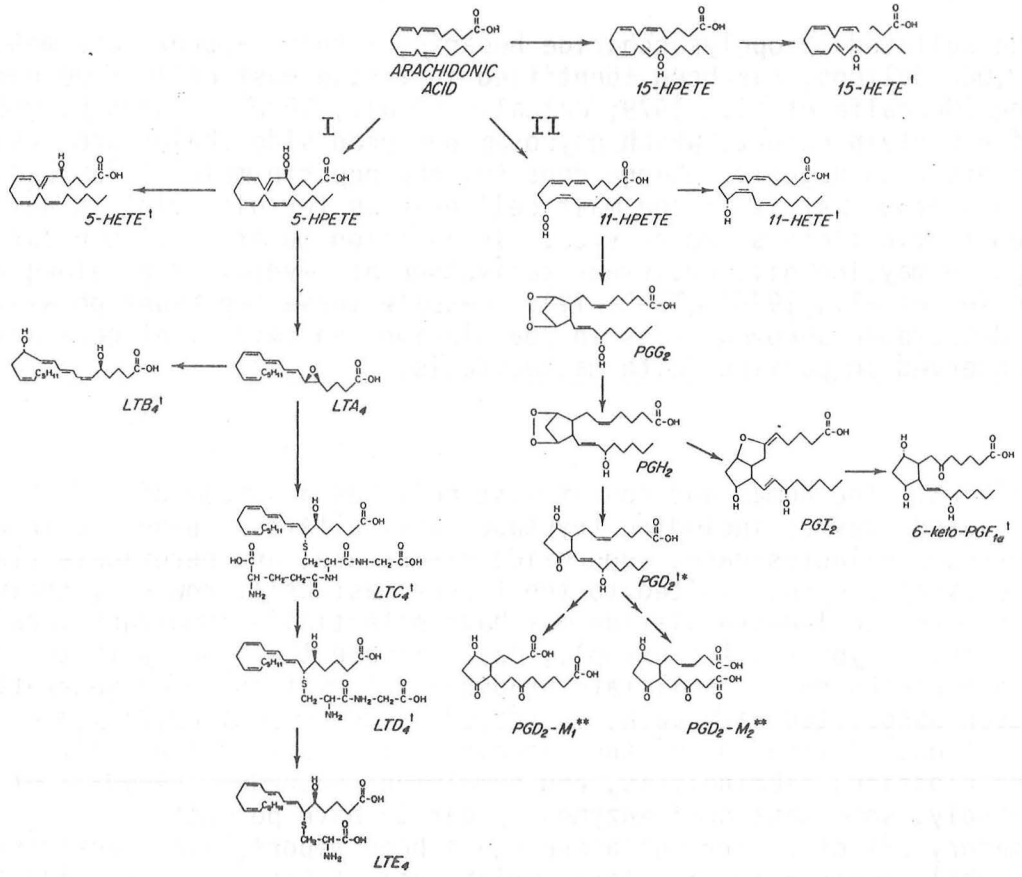


Figure 5. Arachidonic acid metabolism. Leukotriene formation via the lipoxygenase pathway (I). Prostaglandin D_2 (PGD_2) generation per the cyclo oxygenase pathway (II).

Newly-Formed Mediators:

PROSTAGLANDIN D_2: Oxidative metabolism of arachidonic acid via the cycloxygenase pathway in human mast cells leads almost exclusively to the generation of prostaglandin D_2 (PGD_2) (Lewis, et al., 1981) (Fig 5). PGD_2 mimics many of the local and systemic effects of histamine (Table V); yet, its action on various tissues is mediated independently of the histamine receptors. The intradermal administration of PGD_2 results in a whealing response that lasts up to one hour and an the erythematous reaction that may persist for nearly two hours (Soter, 1983). In the lung, PGD_2 locally provokes bronchostriction and pulmonary artery vasoconstriction. The systemic release of this molecule, however, results in episodes of profound hypotension (Roberts et al., 1980)) (Table V). The recent observation of increased PGD_2 production in patients with systemic mastocytosis confirms the clinical relevance of this mast cell mediator.

LEUKOTRIENES: Conversion of arachidonic acid via the 5-lipoxygenase pathway leads to the production of the leukotrienes C, D, and E (formerly termed Slow-Reacting Substance of Anaphylaxis, SRS-A) (Fig 5). Leukotrienes C (LTC_4) and D (LTD_4) have been identified in human lung mast cells (Lewis et al., 1980). Both compounds are potent constrictors of peripheral airway smooth muscles, LTD_4 being approximately 100-fold more active than LTC_4 (Table VI). While both molecules are also vasodepressors; LTC_4 constricts skin blood vessels while LTD_4 relaxes cutaneous vasculature (Drazen, et al., 1980). The overall, physiologic relevance of mast cell-derived leukotrienes in vivo remains unknown since decreasing SRS-A activity is observed with increasingly pure human lung mast cell preparations, (Paterson, et al., 1976).

Table VI

NEWLY-FORMED HUMAN MAST CELL MEDIATORS

Mediator	Arachidonic Acid Metabolic Pathway	Effect
HHT	Cyclooxygenase	Chemotactic for PMNs and Eosinophils
Prostaglandin D_2*	Cyclooxygenase	Contracts smooth muscle Increases vascular permeability Increases cAMP
HETE	Lipoxygenase	Chemotactic for PMNs and Eosinophils
Leukotriene C_4* Leukotriene D_4* Leukotriene E_4	Lipoxygenase	Constricts smooth muscle Increases vasopermeability (D_4) Decreases local skin blood flow (C_4) Vasodepressors Synergistic with histamine Promotes prostaglandin generation

* Demonstrated in human mast cells.

The release of tissue mast cell mediators can result in a wide range of clinical symptoms and signs which 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. The effects of an antigen-IgE mediated signal, for example, are highly dependent upon the rate at which antigen is presented to cell-bound IgE and the efficiency with which it triggers the biochemical events necessary for cellular activation and secretion. In patients experiencing mild, mast cell-mediated symptoms (nonanaphylaxis), the route of antigen presentation, and hence the anatomical site of mast cell stimulation, accounts in great part for the predominant clinical manifestations. For example, airborne-induced allergens frequently provoke symptoms associated with the eyes and respiratory tract while orally ingested antigens often induce symptoms localized to the gastrointestinal tract (Table VII). Similarly, there is a spectrum of clinical manifestations in patients with mastocytosis that appears to be dependent upon the same variables associated with immediate hypersensitivity reactions.

Table VII

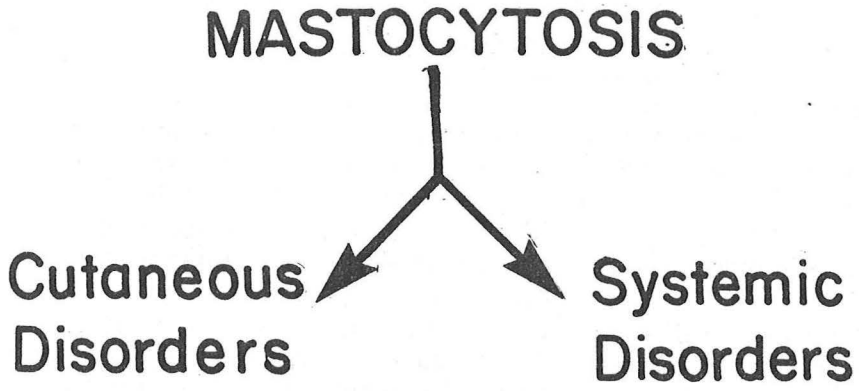
CLINICAL MANIFESTATIONS OF
MAST CELL SECRETION

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

THE MASTOCYTOSIS SPECTRUM

Overview

Mastocytosis is a proliferative disease that results in the abnormal accumulation of mast cells in the skin and, less commonly, other internal organs. It 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. The disorders of mastocytosis can be divided into those with only cutaneous involvement (Cutaneous Mastocytosis), and those associated with mast cell infiltration of several organs (Systemic Mastocytosis) (Fig 6). The reported incidence of mastocytosis in a general patient population ranges from one in 8000 to one in every 1000 patients (Rollier, 1958; Havard and Scott, 1959; Findlay et al., 1960). Recent reports of patients with mastocytosis, however, suggest that this disease is more common than has been previously recognized (Roberts et al., 1982).



The age of onset of mastocytosis is quite variable and extends from birth (Lees and Stroud, 1959; Klaus and Winklemann, 1962) to the eighth decade (Littler, 1966). However, it appears that the disease most frequently occurs in early childhood with approximately 75% of the reported cases being diagnosed within the first two to four years of life (Lees and Stroud, 1959; Caplan, 1963; Klaus and Winklemann, 1962). The age of disease onset may be helpful in differentiating isolated cutaneous from systemic disease. In general, a much higher incidence of systemic mastocytosis is observed in children whose disease persists into adulthood. In addition, adult patients who develop mastocytosis have approximately an eight-fold greater incidence of systemic involvement than children. Mastocytosis occurs in males and females with equal frequency and without any apparent predilection for race. No clearly defined genetic pattern has been established although more than forty different families have been identified in which two or more members have been affected. This includes eight sets of identical twins concordant for the disorder and two monozygotic and two fraternal twin pairs discordant for mastocytosis (Shaw, 1968; Jelenik, 1970; Selmanowitz and Orentreich, 1970; Selmanowitz et al. 1970; Rockoff, 1978). The overwhelming majority of affected patients, however, have no familial association.

Etiology

The etiology of mastocytosis remains unknown although a number of theories (infections, metabolic abnormalities, toxins, and inflammation) have evolved over the years. It also has been postulated that the disorders within the mastocytosis spectrum might result from the development of a neoplastic mast cell clone; however, clinical observations over the last 100 years do not support this theory. Children who develop mastocytosis usually have a self-limited disorder that often resolves before adulthood. Although mastocytosis in adults frequently persists throughout life, these patients rarely die from a neoplastic, mast cell process. This is supported in part by the rare occurrence of mast cell leukemia. Furthermore, tissue mast cells from patients with mastocytosis usually appear normal by transmission electron microscopy. Recently, murine studies have demonstrated that the growth and development of some mast cell populations are largely dependent upon "growth factors" elaborated from T lymphocytes as well as other cells. A number of mast cell growth factors (mast cell growth factor, P cell-stimulating factor, WEHI-3 growth factor, and histamine producing cell stimulating factor) have been identified and partially characterized. It appears, however, that these molecules are very similar, if not identical, to the lymphokine, interleukin 3 (IL-3) (Ihle, et al., 1983). IL-3 appears to be critical for the in vitro development of murine bone marrow-derived mast cells (Nabel et al, 1981; Razin et al., 1982). In addition, studies have indicated that the growth of murine intestinal mast cells are highly dependent upon IL-3-like growth factors. The in vitro growth of mucosal and connective tissue mast cells can be accomplished in the absence of added IL-3, but the presence of embryonic fibroblast feeder layers are required (Ginsburg et al., 1982). This observation suggests that fibroblasts may also elaborate mast cell growth-promoting molecules. It is interesting to speculate that the apparent mast cell proliferative defect in patients with mastocytosis might result from the uncontrolled production of IL-3 or IL-3-like growth factors. Localized cutaneous fibroblast and/or lymphocyte production of IL-3 might account for the well-circumscribed accumulations of mast cells frequently observed in the skin of patients with mastocytosis. Furthermore, disseminated or systemic mast cell disorders might result from an increased production and/or a more general response to such growth-promoting factors. In support of this hypothesis is the observation of increased bone marrow mast cells in several preleukemic and lymphoproliferative disorders (polycythemia rubra vera, myelofibrosis, and acute and chronic leukemias) (Yoo et al., 1978; Prokocimer and Polliack, 1981). To date, the potential role of IL-3 and the cells associated with its production remain an unexplored area of investigation in patients with mastocytosis.

The Clinical Disorders of Mastocytosis

Most, but not all, patients with mastocytosis have demonstrable, persistent cutaneous lesions that can serve as an excellent means for establishing the diagnosis. In fact, the morphology and distribution of these lesions frequently are helpful in differentiating patients with isolated cutaneous disorders from those with systemic involvement. Patients without clinically evident or persistent skin lesions, however, have been described (Ruiz-Maldonado et al., 1975; Roberts et al., 1982), and can present a significant diagnostic challenge

to the clinician. Often such patients have a variety of complaints suggesting several different diagnoses. In this situation, the symptom complex and a high degree of suspicion are the important elements for establishing the presence of a proliferative mast cell disorder.

The purpose of the following sections is to review the clinical manifestations of the disorders within the mastocytosis spectrum, to offer a diagnostic approach for evaluating patients suspected of having this disease, and to outline a rational therapeutic regimen based on our understanding of normal tissue mast cell function.

CUTANEOUS MASTOCYTOSIS

Clinical Symptoms

Patients with abnormal accumulations of mast cells localized to the skin will frequently seek medical attention because of their cutaneous lesions and associated symptoms (Table VIII). Spontaneous, generalized pruritus and localized flushing involving the face, neck, and upper chest occur in some patients with moderate to widespread skin involvement. More severe symptoms such as dyspnea, diarrhea, and syncope are generally associated with extensive cutaneous lesions (Bloom et al., 1958; Demis et al., 1961; Demis, 1963; Brett et al., 1967), although a few patients with solitary skin nodules have been reported to have similar severe symptoms (Brett et al., 1967; Holmberg, 1970). Not uncommonly, these symptoms may be exacerbated by exercise, heat, or local trauma to the lesions. In addition, a variety of compounds including alcohol, narcotics, and salicylates have been implicated in provoking symptoms (Robinson et al., 1962; Sutter et al., 1962).

Table VIII

SYMPTOMS ASSOCIATED WITH CUTANEOUS MASTOCYTOSIS

CUTANEOUS	GI
Pruritus	Nausea
Flushing	Vomiting
	Diarrhea
	Abdominal cramps
CARDIOPULMONARY	**NEUROLOGIC**
Dyspnea	Dizziness
Palpitations	Headache
	Syncope

Cutaneous Signs

The skin lesions most frequently encountered in patients with cutaneous mastcytosis include either 1) a solitary, hyperpigmented nodule or plaque (mastocytoma), or 2) a variable number of hyperpigmented macules and/or papules. The solitary cutaneous form may be present at birth or can arise within several months thereafter. Although this pigmented lesion may occur in any anatomical location, it characteristically involves a distal extremity with a predilection for the wrist area. The macular/papular variant appears to have a much greater range of age onset spanning a period of several weeks after birth to adulthood. This cutaneous pattern is readily appreciated as a variable number of hyperpigmented flat and/or elevated lesions that may be localized to one anatomical area or, more commonly, distributed symmetrically over the cutaneous surface. Usually, however, the macular/papular variant spares the face, palms, and soles.

Both the localized and diffuse forms of cutaneous mastocytosis may urticate spontaneously and occasionally evolve into non-scarring vesicles or bullae. The bullae are usually round, tense, and contain a clear colorless fluid; frequently they arise on an erythematous base. Vesicle or blister formation per se occurs almost exclusively in infants, but greatly diminishes in frequency by three years of age (Demis et al., 1961; Robinson et al., 1962; Caplan, 1963; Orkin et al., 1970). The presence of blisters in patients with mastocytosis does not appear to be a helpful feature for differentiating isolated cutaneous involvement from systemic disease. Mast cell infiltrates in the skin can be confirmed by a simple diagnostic maneuver of firmly rubbing a characteristic lesion. The formation of an urticarial wheal (Darier's sign) at the lesion site is indicative of an abnormal accumulation of cutaneous mast cells and the release of their vasoactive mediators.

Diagnostic Studies

The diagnosis of mastocytosis is best established by a biopsy of a characteristic cutaneous lesion. Utilizing the fluorochrome-avidin technique or a metachromatic stain (toluidine blue or giemsa dye), clusters of granular-appearing mast cells infiltrating the papillary dermis are readily demonstrated in paraffin-embedded sections. It should be noted that a number of disorders other than mastocytosis have been associated with increased cutaneous mast cells (Table IX). However, each of these diseases is readily differentiated from primary mastocytosis by other distinguishing clinical and pathological characteristics.

As expected, the histamine content of characteristic skin lesions in patients with mastocytosis is elevated (Lindell et al, 1961; Winklemann et al., 1966). Elevations in urine and serum histamine levels also have been noted in patients without obvious systemic disease; however, these increased values have not always correlated with apparent disease activity (Demis et al., 1961; Demis 1963, and 1982;; Brogren et al., 1959; Horakova et al., 1977). This is not surprising in light of the observations of Gleich and Hull (1980) who demonstrated the inaccuracy of histamine determinations in many laboratories due to the lack of proper controls. In addition, from our understanding of its

metabolism, urinary histamine in its native form would be expected to represent only 1 to 3% of the total histamine excretion while its metabolite, 1-methyl-4-imidazoleacetic acid (MeIMAA) represents 60-80% of excreted histamine (Fig. 4). Granerus and coworkers (1983) and Keyzer et al. (1983) have demonstrated urinary MeIMAA levels to be an accurate and sensitive marker for elevated histamine concentrations in some patients with mastocytosis. Other laboratory studies in cutaneous mastocytosis patients including a CBC, clotting parameters, liver function tests, and skeletal x-rays are routinely normal.

TABLE IX

DISORDERS ASSOCIATED WITH

INCREASED CUTANEOUS MAST CELLS

Actinic Keratosis	Mastocytosis
Atopic Dermatitis (chronic)	Mycosis Fungoides
Basal Cell Epithelioma	Myxedema
Contact Dermatitis (chronic)	Neurofibromatosis
Erythroderma	Paget's Disease
Lichen Planus	Psoriasis
Lichen Simplex Chronicus	Squamous Cell Carcinoma

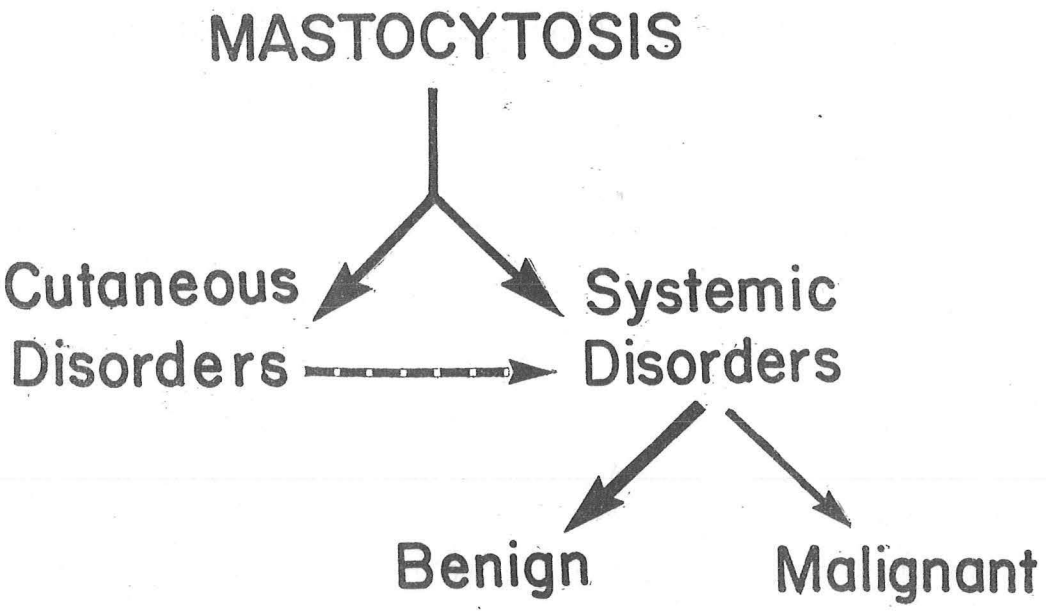
Prognosis

Overall, patients with abnormal accumulations of mast cells localized to the skin appear to have a very favorable prognosis. Solitary lesions, which occur almost exclusively in infants, usually resolve spontaneously after several years (Demis et al.,; Demis, 1982; Caplan, 1963). The prognosis for patients with the macular/papular form appears to vary according to age of onset. Although prospective studies of thoroughly evaluated patients with this disorder are lacking, retrospective analysis and isolated reports suggest that approximately 80% of the children with the macular/papular pattern will be markedly improved or clear of their disease by early adulthood (Lees and Stroud, 1959; Klaus and Winklemann, 1962; Caplan, 1963). Information relating to the adult-onset mastocytosis group with the macular/papular variant is less clear, and may reflect the rarity of this cutaneous pattern without systemic involvement in this age group. In general, adult patients with macular/papular mastocytosis tend to have a chronic disease with a significant likelihood for eventual systemic progression (Sagher and Even-Paz, 1967).

SYSTEMIC MASTOCYTOSIS

The term systemic mastocytosis implies an aberrant accumulation of mast cells in several organs which frequently includes the skin. This disorder represents approximately 10% of all patients within the mastocytosis spectrum, and although it has been identified in all ages, adults appear to have approximately an eight-fold greater incidence of extracutaneous involvement than children. Children whose disease persists into adulthood, however, also are more likely to develop a systemic process. (Sagher and Even-Paz, 1967).

Two forms of systemic mastocytosis exist, a benign form that remains relatively static and is characterized by mast cell infiltration of one to several extracutaneous sites, and a malignant form that is typified by uncontrolled mast cell proliferation and widespread organ involvement (Lennert and Parwaresch, 1979). Patients with benign systemic mastocytosis generally enjoy relatively good health; however, they often are plagued chronically by recurrent symptoms associated with mast cell-mediator release and/or by the side effects of medications employed for the treatment of these symptoms. Mastocytosis patients with a more malignant process are less fortunate with most developing a fatal, often mast cell leukemia-like, disorder. Fortunately, this form of mastocytosis is uncommon.



The ability to clinically differentiate systemic involvement from the isolated cutaneous disorders is of important prognostic significance since the malignant form of mastocytosis normally arises in patients with pre-existing extracutaneous disease. By taking into account the patient's age, certain symptoms and signs can provide the clinician with a useful set of guidelines for identifying patients with systemic involvement.

Clinical Symptoms

The wide range of symptoms associated with cutaneous mastocytosis is also observed in patients with systemic disease (Table X). While initially many of these symptoms may appear to be unrelated, most can be attributed to the widespread physiologic effects of secreted mast cell mediators. Symptoms that may signal the presence of extracutaneous involvement include: fever, malaise, weight loss, bone and/or epigastric pain, and disorders in mentation (cognitive disorganization).

TABLE X

SYMPTOMS ASSOCIATED WITH SYSTEMIC MASTOCYTOSIS

CUTANEOUS	NEURO
Pruritus	Dizziness
Flush	Headache
Hives	Syncope
	Cognitive disorganization*
GI	**OTHERS**
Nausea	Fever*
Vomiting	Malaise*
Diarrhea	Weight loss*
Epigastric pain*	Bone pain*
CARDIOPULMONARY	
Dyspnea	
Palpitations	

* Symptoms helpful in differentiating systemic from cutaneous mastocytosis.

Clinical Signs

A careful physical examination can be most beneficial in identifying patients with systemic mastocytosis. Several distinct cutaneous patterns have been associated with systemic involvement and include: 1) widespread hyperpigmented macules and papules, 2) discrete telangiectatic, pigmented macules, 3) erythroderma, 4) diffuse, infiltrative plaques and nodules, and 5) dermographism associated with episodic flushing (Table XI). The hyperpigmented macular/papular variant is indistinguishable from that seen in isolated cutaneous disease; however, when these skin changes are observed in an adult patient, the likelihood of systemic involvement is significantly increased (Sagher and Even-Paz, 1967). The telangiectatic form is readily identified by discrete, reddish-brown macules with overlying telangiectasias. Frequently, these lesions are distributed symmetrically over the trunk and proximal extremities and spare the face, palms, and soles (Stark et al., 1956; Poppel et al.,1959; Sagher and Even-Paz, 1967). The uncommon erythrodermic form of mastocytosis intially appears as widespread and confluent erythematous cutaneous macules (Demis et al, 1961; and Demis 1963 and 1982; Sagher and Even-Paz, 1967). Clinically, this disorder often can not be readily differentiated from other causes of genralized erythroderma. However, with time these cutaneous lesions may become more infiltrative and frequently evolve into small, pruritic, yellowish-red papules. With continuous scratching, large yellow to tan, lichenified plaques develop diffusely over the trunk and extremities resulting in a striking "grained-leather" skin appearance. These changes are often accentuated in the intertriginous areas, and have a characteristic doughy feeling. Because of the yellow skin hue, this infiltrative form of mastocytosis has been likened to xanthematous infiltrates, hence the descriptive terms xanthelasmoidea and pseudo-xanthomatous mastocytosis (Table I). (Waters and Lacson, 1957; Griffiths and Danesbod, 1975; Meneghini and Angelini, 1980; Willemze et al., 1980). As in patients with isolated cutaneous mastocytosis, a positive Darier's sign usually can be elicited over characteristic skin lesions in patients with systemic disease.

TABLE XI

CUTANEOUS PATTERNS ASSOCIATED
WITH SYSTEMIC MASTOCYTOSIS

Hyperpigmented macules/papules
Telangiectatic pigmented macules
Erythroderma
Diffuse infiltrative plaques/nodules
Dermographism/Flushing

An additional group of systemic mastocytosis patients has been identified more recently, and is noteworthy by the lack of persistent cutaneous lesions (Ruiz-Maldonado, et al., 1975; Roberts et al., 1982; Kendall et al., 1984). Most of these patients experience recurrent episodes of flushing localized to the face, neck, and upper chest. In nearly all, dermographism can be elicited, and approximately one-third experience an evanescent, erythematous papular eruption (Roberts et al, 1982). Because they lack persistent cutaneous lesions, this patient subset has been described as having "occult mastocytosis". An important clue to making the diagnosis in these patients is a characteristic constellation of clinical symptoms suggesting a mast cell-associated disorder (Table XII).

Table XII

CLINICAL MANIFESTATIONS OF OCCULT MASTOCYTOSIS

Symptoms and Signs	% Incidence (19 pts)
Syncope/Dizziness	100
Hypotension	100
Flushing	95
Pruritus	95
Palpitations/Tachycardia	90
Abdominal Cramps/Diarrhea	75
Nausea/Vomiting	50
Headaches	50
Dyspnea	50
Wheezing	0

Roberts et al., 1982

TABLE XIII

CUTANEOUS SIGNS OF OCCULT MASTOCYTOSIS

Dermographism
Flushing
Evanescent red papules

Roberts et al., 1982

Organ Involement

Although systemic mastocytosis may involve any organ, the skin, liver, spleen, lymph nodes, and gastrointestinal tract are preferentially involved. Thus, additional important clinical signs of systemic involvement include the findings of hepatomegaly, splenomegaly, lymphadenopathy, and localized bone and/or epigastric tenderness (Table XIV). (Sagher and Even-Paz, 1967; Roberts et al., 1980; Lennert and Pawaresch, 1979; Webb et al., 1982).

LIVER: In two different series, approximately 70% of the patients with systemic disease had demonstrable hepatomegaly at the time of diagnosis (Lennert et al., 1962; Sagher and Even-Paz, 1967). Webb and co-workers (1982), however, recently found that only 45% of their systemic mastocytosis patients had liver enlargement (Table XIV). Mast cell infiltration of the liver is best detected by percutaneous biopsy, and is most commonly localized to the portal areas. A variable number of eosinophils also are frequently observed accompanying the mast cell infiltrate. Liver function tests in patients with systemic mastocytosis are usually within the normal range, despite clinical evidence of organ involvement (Capron et al., 1978; Fishman et al., 1979). Although extensive fibrosis and portal hypertension have been reported, progressive liver disease is an extremely uncommon complication in this disorder (Capron et al., 1978).

SPLEEN: Spleen enlargement also is an important clinical sign of systemic involvement. In three different series, 50% or more of the patients with systemic mastocytosis were noted to have splenomegaly (Table XIV). Although significant splenic enlargement has been reported in some patients, hypersplenism is a rare complication of this disorder. The effects of mast cell infiltrates in the spleen may range from changes in architectural pattern to total ablation of normal spleen morphology (Sagher and Even-Paz, 1967; Lennert and Parwaresch 1979). Eosinophils often are observed among these mast cell infiltrates (Webb et al., 1982).

LYMPH NODES: Peripheral lymphadenopathy is less common than either hepatomegaly or splenomegaly with a reported patient incidence ranging from 28% to 40% (Table XIV). Localized lymphadenopathy is more frequently detected than is generalized nodal enlargement in patients with "benign" systemic mastocytosis. In two different series (Lennert, 1962; Webb et al., 1982) pathological examination of nodes from different sites indicated that mast cell infiltrates were most commonly observed in abdominal lymphs nodes, whereas peripheral nodes provided, at best, only a suspicion of involvement. When lymphadenopathy is clinically detectable, both liver and spleen enlargement are usually evident. Histologically, the normal architecture of affected nodes is often preserved even in the presence of dense mast cell infiltration. Occasionally, fibrotic changes similar to those noted in the liver and spleen have been reported (Littler, 1966; Webb et al., 1982). As seen in other organs, eosinophils frequently accompany mast cell infiltrates in lymph node tissue.

TABLE XIV

CLINICAL SIGNS ASSOCIATED WITH SYSTEMIC MASTOCYTOSIS

	Incidence (percent)		
	Lennert (1962)	Sagher and Even-Paz (1967)	Webb et al. (1983)
	(21 pts)	(71 pts)	(25 pts)
Hepatomegaly	71%	72%	45%
Splenomegaly	81%	62%	50%
Lymphadenopathy	---	28%	40%

BONE MARROW: Historically, the diagnosis of systemic mastocytosis has been substantiated by observing increased tissue mast cells in bone marrow specimens. In a group of systemic mastocytosis patients reviewed by Sagher and Even-Paz (1967), abnormal accumulations of mast cells were noted in 90% of the bone marrow aspirates or biopsies examined. Webb and coworkers (1982) reported an even higher incidence of marrow involvement in their systemic mastocytosis population with all 25 patients clearly having abnormal accumulations of tissue mast cells. Mast cell infiltrates within the marrow frequently are localized to paratrabecular or perivascular areas, and often are accompanied by an eosinophil infiltrate. The overall mast cell morphology in the marrow of patients with benign systemic mastocytosis is usually normal. Immature or granular, monocytoid cells observed in the bone marrow of patients with mastocytosis is an ominous sign, and usually indicates a more malignant process (Lennert and Parawaresch, 1979). It should be noted that in addition to systemic mastocytosis, increased bone marrow mast cells are observed in a number of hematologic diseases (Table XV). Thus, the presence of mast cells in the bone marrow alone is not sufficient for the diagnosis of systemic mastocytosis.

TABLE XV

DISORDERS ASSOCIATED WITH

INCREASED BONE MARROW MAST CELLS *

Mastocytosis
Acute myeloblastic leukemia
Chronic lymphocytic leukemia
Erythroleukemia
Lymphocytic Lymphoma
Histiocytic Lymphoma
Waldenstrom's macroglobulinemia
Sideroblastic anemia
Polycythemia rubra vera

* Adopted from Prokocimer and Polliack (1981) and Lennert and Parwaresch (1979).

With a high incidence of bone marrow involvement, patients with systemic mastocytosis would be expected to have abnormalities in the peripheral blood. Although no characteristic or consistent changes have been associated with this disorder, 46% to 62% of the patients with systemic mastocytosis have some demonstrable hematologic abnormality. Table XVI compares the peripheral blood findings of patients with systemic mastocytosis in two different series with Anemia, leukocytosis, and/or thrombocytopenia were the most commonly detected abnormalties. Persistent elevations in the white blood cell count ($>20,000/mm^3$) and/or the presence of mast cells in the peripheral circulation are two important findings that may indicate the presence of a more malignant process (Friedman et al., 1958; Efrati et al., 1957; Sagher and Even-Paz, 1967, Webb et al., 1982).

TABLE XVI

HEMATOLOGIC FINDINGS IN PATIENTS

WITH SYSTEMIC MASTOCYTOSIS

	Incidence (%)	
	Sagher and Even-Paz (71 pts)	Webb et al. (24 pts)
Anemia	42	37
Leukocytosis	18	29
Thrombocytopenia	21	22
Eosinophilia	12	17
Monocytosis	7	17
Leukopenia	13	15
Basophilia	2	0
Lymphocytosis	2	0

BONE: Skeletal involvement has been reported to occur in 65% to 70% of the patients with benign systemic mastocytosis. Clinically, the identification of localized, painful bone lesions on physical examination should alert the clinician to skeletal involvement. Radiographically, two types of bone involvement are recognized, a limited type in which only a few, well-circumscribed lesions are detectable, and a diffuse type that is characterized by widespread, poorly-defined bony involvement. In the limited disorder, which is seen in approximately 25% of systemic mastocytosis patients, circumscribed osteosclerotic and/or osteoporotic areas are frequently detected in the skull and long bones. These focal areas of mast cell infiltrates rarely progress and may actually resolve spontaneously (Sagher and Even-Paz, 1967). The diffuse type of bone involvement is more common (approximately 75% of all bony lesions), and usually results from an admixture of osteolytic and osteoblastic activity that radiographically assumes a reticulated or "ground-glass" appearance.

Frequently such bony involvement is widespread and primarily involves the skull, vertebral column, ribs, and pelvis. This type of skeletal involvement may remain static, or it may progress at a variable rate. In patients with the progressive type of osteoporosis, pathologic fractures have been reported (Rafii et al., 1983). The pathophysiology of these skeletal changes are not well-understood, but mast cell mediators are believed to play a central role. Histamine has been demonstrated to stimulate fibrous tissue formation that ultimately may be converted into osteoid layers for calcium salt deposition (Gagnon et al., 1975; Hentzer et al., 1980). Conversely, the release of stored mast cell heparin may promote the osteoporosis associated with this systemic disease. Heparin has been implicated in facilitating bone resorption, and reports of vertebral compression fractures resulting from progressive osteoporosis have been described in patients receiving therapeutic doses of heparin (Griffith et al., 1965; Jaff and Willis, 1965; Thompson R, 1973). In addition, the release of PGD_2 from human mast cells has been proposed to act in conjunction with heparin to promote bone resorption. Taken together, these observations suggest that mast cell mediators may influence bone metabolism, and may play a role in the skeletal lesions of patients with mastocytosis.

G.I. TRACT: Infiltration of tissue mast cells in the lower mucosa and upper submucosa areas of the gastrointestinal tract has been demonstrated in a number of patients with systemic mastocytosis (Fishman et al., 1979; Broitman et al., 1970; Dantzig, 1975). Because histamine is a known potent agonist for gastric acid secretion, local accumulations of gut mast cells might be expected to augment normal stomach acid production. Both gastrin hyperacidity and gastrointestinal hemorrhage have been documented in patients with systemic involvement (Keller and Roth, 1970; Belcon et al., 1980; Bredfeldt et al., 1980); however, the occurrence of peptic ulcer disease among all patients with mastocytosis (cutaneous and systemic disorders) has been reported to fall within the range expected for the general population (Ammann et al., 1976; Van Kammen, 1974). Although the true incidence of ulcer disease in systemic mastocytosis remains undefined, Demis (1963) has indicated that patients with the cutaneous telangiectatic pattern of mastocytosis may have an increased tendency for peptic ulcer formation. Thus, the possibility of systemic involvement should be considered in patients with mastocytosis who have clinical manifestations of ulcer disease. Mast cell infiltration and villous atrophy also have been reported in association with intestinal malabsorption in patients with systemic mastocytosis (Broitman et al., 1970; Dantzig, 1975). Malabsorption of D-xylose, glucose, lactose, and vitamin B_{12} have been documented in these patients; however, the mechanism for this rare occurrence is unknown (Ammann, 1976).

DIAGNOSTIC STUDIES

The diagnosis of systemic mastocytosis is dependent upon the demonstration of increased mast cells within various tissues and often requires the use of several diagnostic studies. Cutaneous involvement in systemic mastocytosis is best documented by a skin biopsy with greater than twelve mast cells per high power field being regarded as abnormal (Roberts et al., 1982; Kendall et al., 1984). It is important to emphasize that the proper identification of tissue mast cells requires staining either by the conjugated-avidin technique (Bergstresser, et al., 1984) or the use of basic dyes such as toluidine blue or giemsa. In patients suspected of having systemic mastocytosis, but who lack persistent cutaneous lesions (occult mastocytosis), a skin biopsy from a normal appearing area of the back may demonstrate abnormal mast cell accumulations (Roberts et al., 1982). Our experience with random skin biopsies in such patients has not been as rewarding. We have seen two patients with the clinical manifestations of occult disease (Tables XII and XIII), however, who have had three to four telangiectatic, hyperpigmented macules localized to the lower lateral trunk area. In both patients, random skin biopsies from the back contained normal mast cell numbers while the lesions along the lateral trunk had marked mast cell infiltrates.

Approximately one-third of the patients with systemic disease will have an abnormal CBC with anemia, leukocytosis and/or thrombocytopenia being noted most frequently (Table XVI). Pancytopenia associated with hypersplenism has been reported to occur only rarely in this disorder (Webb et al., 1982).

Although liver involvement has been documented in at least half of the patients with systemic mastocytosis, alterations in liver function tests are uncommon (Table XVII). However, when serologic abnormalities occur, they are likely the result of hepatic mast cell infiltrates.

The detection of increased circulating mast cell mediators and/or their metabolites offers strong, indirect evidence for a proliferative mast cell disorder. Recent studies in patients with mastocytosis have shown that unmetabolized, urinary histamine levels increase above normal values following a symptomatic episode (Turk et al.; 1983; Kendal et al., 1984). Granerus and coworkers (1981) and Keyzer et al. (1983) have demonstrated a persistent elevation of the major urinary histamine metabolite, MeIMAA, (Fig. 4) in patients with mastocytosis. Keyzer reported eight mastocytosis patients in whom he found an increase in the urinary excretion of both methylhistamine and MeIMAA. Simultaneous determinations of unmetabolized urinary histamine levels were abnormal in only three of these eight patients. Granerus et al., (1983) studied 30 patients with mastocytosis and compared MeIMAA values with extent of disease involvement. Patients with cutaneous mastocytosis had significantly lower levels of MeIMAA than those with widespread systemic involvement (Fig. 8). From these studies, it appears that the measurement of urinary MeIMAA is a sensitive and accurate method for indirectly determining elevated histamine production. This quantitative technique may serve as a useful tool for differentiating patients with cutaneous mastocytosis from those with systemic involvement.

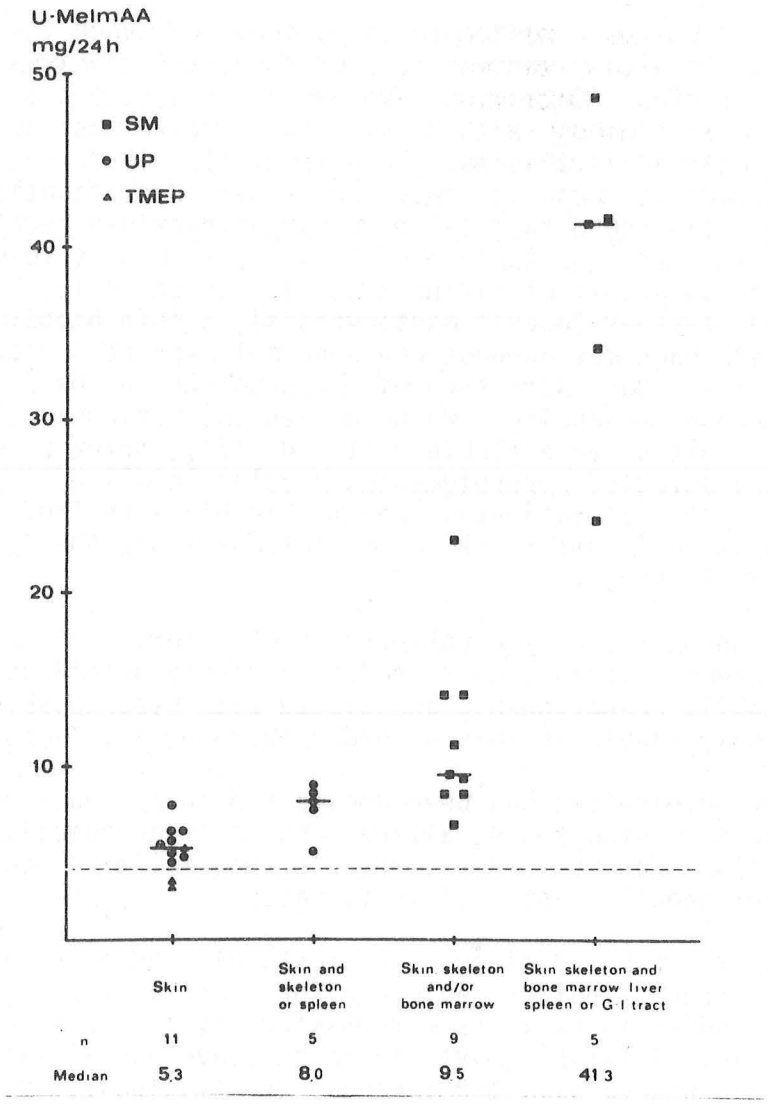


Fig. 8. Urinary methylimidazoleacetic acid (MeIMAA) levels in patients with mastocytosis.

Although mast cells are known to store significant amounts of preformed heparin, patients with systemic disease usually do not have detectable clotting abnormalities. There are, however, a few isolated reports of a "heparin-like material" detected in the circulation of mastocytosis patients following localized trauma to cutaneous lesions (Urbach et al., 1955; Vilanova et al., 1961) and after generalized (mast cell mediated) systemic reactions (Simone and Hayes, 1971; Campbell et al., 1979, and Nenci et al., 1982) (Table XVII).

TABLE XVII

DIAGNOISTIC STUDIES IN PATIENTS
WITH MASTOCYTOSIS

	Mastocytosis	
Diagnostic Study	Cutaneous	Systemic
Skin biopsy	↑ mast cells	↑ mast cells
CBC	normal	normal
Clotting parameters	usually normal	usually normal
Liver function tests	normal	normal
Urine: MeIMAA	↑	↑
PGD_2M	?	↑
Skeletal X-rays	normal	often abnormal
Upper GI Series	normal	may be abnormal
Bone Marrow Biopsy	normal	↑ mast cells

Increased production of the newly-formed mast cell mediator PGD_2 also has been reported in some patients with systemic mastocytosis (Table XVIII). Roberts and co-workers (1980,1982) demonstrated elevated levels of a PGD_2 metabolite (PGD_2M) in the urine of patients with occult disease that led them to direct their therapy at inhibiting prostaglandin formation. This therapeutic approach has proven virtually life-saving for some patients. At present, the measurement of PGD_2M requires a laborious, mass spectrometric method; however, the development of a more rapid assay should provide a powerful tool for identifying patients with mastocytosis, especially those with occult disease.

Table XVIII. Histamine and PGD_2M Levels in a Patient with Mastocytosis.

Value of biochemical parameter	Urine histamine-to-creatinine ratio*	Urine PGD_2 metabolite-to-creatinine ratio*
At time of diagnosis	96	6300
During episode of hypotension	681	10000
During convalesence	32	660
Upper limit of normal range	32	400

*Ratios are calculated as the total amount in micrograms of histamine or in nanograms of PGD-M divided by the total amount in grams of creatinine in a timed (6 to 24 hr) collection or urine.

Radiographic studies are often useful in evaluating patients suspected of having systemic involvement. As discussed earlier, skeletal x-ray abnormalities occur in nearly two-thirds of the patients with systemic disease with a diffuse, reticulated or "ground-glass" appearance being noted most frequently. The use of radionucleotide bone scans also may be useful as a screening tool in patients suspected of having skeletal involvement (Sostre and Handler, 1977; Soter et al., 1979). Contrast studies of the gastrointestinal tract (GI) have been reported to be abnormal in some patients with systemic mastocytosis. Gastric and duodenal ulcerations, exaggerated mucosal folds, and motility disturbances have been noted (Ammann et al., 1976; Clemett et al., 1968; Belcon et al., 1980; Campbell et al., 1979) (Table XVII). Roberts and coworkers (1982) reported that nearly half of their patients with occult mastocytosis had multiple 1-3 mm nodular mucosal filling defects on an upper GI series. It is uncertain if these radiographic changes represent focal accumulations of mast cells in the GI tract and/or local gut wall edema resulting from mediator release. None of these radiographic changes described are specific for systemic mastocytosis; however, they often are useful in the evaluation of patients suspected of having extracutaneous involvement.

In general, the need for more invasive diagnostic procedures in mastocytosis patients is rarely warranted; however, occasionally a bone marrow, liver, and/or gastrointestinal biopsy may be required to establish the presence of a systemic process. Previous reports suggest that bone marrow specimens obtained by the biopsy technique are preferable to the aspiration method for accurately determining the number of tissue mast cells. In mastocytosis patients with marrow involvement, mast cells frequently aggregate into clumps and/or adhere to fibrous tissue in the marrow, making bone marrow aspiration technically difficult and highly inaccurate (Havard and Scott, 1959; Sagher and Even-Paz, 1967). Advances in endoscopic procedures have provided a direct and safe method for obtaining gastrointestinal tissue. Should this procedure become necessary, increased mast cells are more likely to be observed in specimens obtained from mucosal areas with urticarial wheals, hyperemia, and/or ulcerations. (Clemett et al., 1968; Ammann et al. 1976, and Belcom et al., 1980).

Prognosis

The overall prognosis for patients with systemic mast cell disease is less favorable than for those with an isolated cutaneous disorder. Although the mortality appears to be relatively low, the morbidity of chronic, poorly controlled symptoms is significant. A small, and unpredictable, subset of patients with extracutaneous involvement will progress to a more malignant and ultimately fatal process (Sagher and Even-Paz, 1967; Lennert and Parwaresch, 1979).

Malignant Systemic Mastocytosis

The term malignant systemic mastocytosis is reserved for those patients with immature appearing mast cells in tissues and peripheral blood. This malignant process may develop de novo, however, more often, it represents a transition from a benign systemic disease to an aggressive and ultimately fatal disorder. It has been estimated that as many as one-third of the patients with benign systemic mastocytosis will develop a more malignant process. However, this figure seems exaggerated by the fact that less than 40 well-documented cases of malignant mastocytosis have been reported in the literature. Although far more common in adults, this aggressive mast cell disorder occurs in all age groups, with a peak incidence around the sixth and seventh decades. (Waters and Lacson, 1957; Friedman et al., 1958; Sagher and Even Paz, 1967; Lennert and Parwaresch, 1979).

Historically, patients who develop malignant disease initially have typical signs and symptoms of benign systemic mastocytosis (Table XI and Table XIV). The transition from a benign to a malignant disorder is frequently detected first in the peripheral circulation with worsening of a pre-existing anemia and/or a rise in the white blood cell count (>20,000 mm^3). In patients who develop a true mast cell leukemia, typical, and later, atypical mast cells appear in the peripheral blood. Approximately one-third of the patients with malignant mastocytosis, also develop a myeloid or monocytic leukemia prior to their death (Ultmann et al., 1964; Lennert and Parwaresch, 1979). Post-mortem examination of these patients usually demonstrates widespread organ infiltration of tissue mast cells. To date, no prognostic parameters have been identified that permit the early detection of individuals predisposed to developing this malignant disorder.

TREATMENT OF MASTOCYTOSIS

Patients with solitary accumulations of cutaneous mast cells usually require no therapeutic intervention by the fact that most lesions resolve spontaneously (Caplan, 1963; Sagher and Even-Paz, 1967). However, in those few patients who have associated systemic symptoms, lesional excision, which is curative, should be performed.

To date, therapy for patients with either extensive cutaneous disease or systemic involvement is purely supportive. Unfortunately, controlled studies examining the effects of different therapeutic modalities alone or in combination in this patient population are lacking. Hence, most information regarding the response to various treatments is derived from small, uncontrolled series or isolated case reports.

AVOIDANCE OF POTENTIAL MAST CELL SECRETAGOGUES: At the time of diagnosis, patients with mastocytosis should be cautioned about the potential for some drugs and medications to provoke mast cell mediator release, and thus, exacerbate their clinical disease. Alcohol, anticholinergic preparations, aspirin, narcotics, and polymyxin B have been implicated in triggering systemic symptoms (Sutter et al., 1962; Harmin, 1957; Wyre and Henrichs, 1978; Kaye and Passero, 1979). It appears that patients with isolated cutaneous disease or systemic involvement are at equal risk to developing an adverse reaction to any of these agents.

HISTAMINE ANTAGONISTS: Because mast cell histamine is known to exert profound physiologic effects on blood vessels, cardiac tissue, and bronchial and intestinal smooth muscle, (Table IV), the use of histamine antagonists is important in the treatment of mastocytosis patients. Since both H_1 and H_2 receptors are present in a number of tissues, it is predictable that the combined use of a H_1 antihistamine (hydroxyzine, diphenhydramine or chlorpheniramine) and a H_2 antagonist (cimetidine or ranitidine) would be superior to either alone for controlling histamine-related symptoms (Table V). Gerrard and Ko (1979) and Simon (1980) reported this combination therapy to be effective in relieving a number of symptoms in their mastocytosis patients. In addition, Hirschowitz and Groarke, (1979), noted that H_2 antagonist therapy was beneficial in controlling gastric acid hypersecretion, but not diarrhea, in two patients with systemic mastocytosis.

An alternative to conventional antihistamine preparations is the use of tricyclic antidepressants, which are known potent histamine antagonists (Richelson, 1979). On a molar basis, the antidepressant doxepin is nearly 800-fold more potent at the H_1 receptor *in vitro* than diphenhydramine (Table XIX). More recently, Sullivan (1982) has demonstrated the utility of this drug *in vivo* for its antihistaminic effects. Our own experience indicates that patients with systemic mastocytosis require from 20 to 100 mg/d of doxepin (split in a bid dosage) for the control of histamine-mediated symptoms. Although doxepin also appears to be a potent H_2 antagonist, the utility of the this medication for relieving gastrointestinal symptoms remains undocumented.

TABLE XIX

TRICYCLIC ANTIDEPRESSANT AFFINITIES

FOR HISTAMINE RECEPTORS:

COMPARISON WITH SELECTIVE ANTAGONISTS

	Histamine Receptor	
Drug	H_1	H_2
Tricyclic Antidepressants		
Doxepin	3,100	0.6
Amitriptyline	770	2.2
Histamine Antagonists		
Pyrilamine	50	
Diphenhydramine	4	
Cimetidine		0.1
Metiamide		0.1

Richelson, 1983

PROSTAGLANDIN INHIBITORS: While combination H_1 and H_2 antihistamine therapy has proven beneficial is controlling the symptoms of some mastocytosis patients, others have been refractory to this treatment regimen (Roberts et al., 1980; Roberts et al., 1982). The identification of elevated PGD_2M levels in the urine of some patients with life-threatening disease led Roberts and his coworkers (1980; 1982) to employ aspirin (as an inhibitor of PGD_2 synthesis) in combination with H_1 and H_2 antihistamine therapy. This combined therapeutic approach resulted in a dramatic cessation of life-threatening, hypotensive episodes. Paralleling this clinical response was a marked diminution in detectable urinary PGD_2M levels (Table XVIII). Because of the mast cell-secretagogue potential of both aspirin and NSAIA (Hammin, 1957; Roberts et al., 1982), it is most prudent to initially treat patients with a combination of H_1 and H_2 antihistamines. If no therapeutic response is evident, then very small doses of aspirin (40 mg/d) may be added and increased gradually until plasma salicylate levels rise to 20-30 mg/dl (approximately 3.9 - 5.2 gm of aspirin/d) (Roberts et al. 1982). To avoid potential gastric irritation, enteric-coated aspirin is recommended.

TABLE XX

RESPONSE OF PATIENTS WITH MASTOCYTOSIS TO ASPIRIN THERAPY*

Patients (15)	Clinical Course
12/15	No or few symptoms
1/15	Mild symptoms
2/15	Hypotension

* Aspirin dosage (3.2 - 5.9 gm/d)
Roberts et al., 1982

DISODIUM CROMOGLYCATE: Disodium cromoglycate (DSCG) is effective in controlling mast cell-mediated, type I allergic reactions in the lung (Cox, 1971); however, this compound is less effective in suppressing experimental-induced mast cell degranulation in the skin (Assem and Mongar, 1970). While its mode of action is incompletely defined, DSCG is thought to prevent mast cell mediator release by interfering with calcium transport across the cell membrane. Although less than two percent of orally administered DSCG is absorbed, this medication has proven efficacious in alleviating some of the clinical manifestations associated with mastocytosis. In an original observation, Dolovich and coworkers (1974) reported complete inhibition of persistent diarrhea with oral DSCG in a mastocytosis patient. Later Soter et al. (1979) in a double-blind, crossover study, demonstrated the therapeutic effects of DSCG in three out of four mastocytosis patients tested. In addition to eliminating diarrhea and abdominal pain, 400 mg/d of oral DSCG provided relief of cutaneous symptoms (itching, urtication and flushing) and central nervous system dysfunction (cognitive disorganization (Fig. 9). This preparation, taken orally, also has proven effective in controlling the bullous eruption of mastocytosis in infants (Welch et al., 1983). A drug similar to DSCG but superior in its gastrointestinal absorption, ketotifen, recently has been shown in a double-blind study to also control the cutaneous manifestations (pruritus and urtication) of mastocytosis (Czarnetzki, 1983). In the author's opinion, ketotifen was more efficacious in relieving patients' symptoms when compared to DSCG. Experience with this drug in the United States is lacking since it is not yet available for general use.

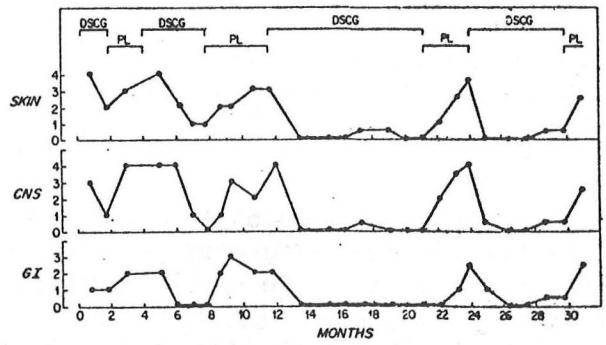


Fig. 9 Time Course of Effect of Disodium Cromoglycate and Placebo in Patient 1.

The symptoms and signs are represented semiquantitatively: 0, absent; ±, minimal; 1+, mild; 2+, moderate; 3+, severe; and 4+, incapacitating. CNS and GI denote, respectively, the central nervous system and the gastrointestinal tract.

PSORALENS, UVA (PUVA): The use of 8-methoxypsoralen and long wave ultraviolet irradiation (PUVA) may be efficacious in controlling the pruritus and cutaneous whealing in mastocytosis patients. Christophers and coworkers (1978) used PUVA therapy four-times-weekly in 10 patients with mastocytosis. After four to five weeks, symptomatic improvement was evident. This coincided with a decrease in a demonstrable Darier's sign. Within three to six months of discontinuing treatment, however, two of five patients seen in follow-up had a relapse of their symptoms. Granerus et al. (1981) also reported symptomatic improvement in three patients with systemic mastocytosis after 10-12 weeks of PUVA therapy. Concomitant with this subjective response was a significant decrease in both the number of cutaneous mast cells and the level of MeIMAA excretion. Three months after discontinuing treatment, all three patients were still free of symptoms. James (1982) also noted a reduction in pruritus after treating five mastocytosis patients with PUVA. However, like Christophers (1978), recurrence of pruritus and urtication was observed in these patients after cessation of therapy. Thus, in most patients, it appears that the chronic administration of PUVA is necessary for symptomatic relief. In view of the potential hazards of long-term PUVA therapy, it is most prudent to restrict the use of this treatment to patients not responding to a combination of other therapeutic modalities (antihistamines, salicylates and/or DSCG). Short-term PUVA therapy, however, may be effective for relieving intractable pruritus and urtication.

CORTICOSTEROIDS: The use of corticosteroids in the treatment of mastocytosis is uncontrolled, but relief of cutaneous and gastrointestinal symptoms have been noted (Sagher and Even-Paz, 1967; Fishman et al., 1979). Systemic corticosteroids administered to dogs with cutaneous mastocytosis have been reported to decrease mast cell infiltrates (Bloom et al., 1952). Corticosteroids injected into skin lesions of mastocytosis patients also reduce the number of infiltrating mast cells. Taken together, these observations suggest that corticosteroids may have a direct effect on mast cell growth and development. Further studies are required to substantiate these preliminary observations;

however, if correct, the use of systemic corticosteroids, possibly in combination with other chemotherapeutic agents, might prove efficacious in the early treatment of malignant mastocytosis.

EPINEPHRINE: Some patients with systemic mastocytosis may experience recurrent life-threatening episodes of hypotension following mast cell mediator release (Roberts et al., 1980; Turk et al, 1983). The use of epinephrine, which is regarded as a "first-line drug" during acute anaphylaxis, also may be life-saving in these patients. Turk and coworkers (1983) have reported the successful reversal of severe hypotensive episodes with epinephrine in two patients with systemic mastocytosis; however, both patients required repeated administrations of this adrenergic agonist for blood pressure control (Fig. 10). Preliminary studies indicate that the early administration of epinephrine may abort severe attacks of flushing and hypotension (Turk et al., 1983); thus, patients who experience such episodes should be given a premeasured epinephrine preparation to carry for emergency use.

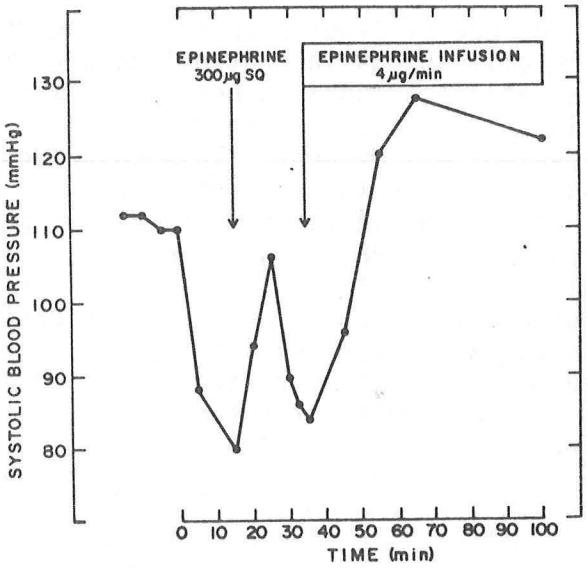


Fig. 10. Blood pressure response of a symptomatic patient with mastocytosis to epinephrine

From our current understanding of the tissue mast cell and its mediators, symptomatic treatment of patients with mastocytosis logically dictates a combination of therapeutic agents. The use of H_1 and H_2 antihistamines in combination with a cyclooxygenase inhibitor (aspirin) is a reasonable approach in patients unresponsive to antihistamines alone. The addition of oral DSCG may prove particularly beneficial for controlling cutaneous, GI, and CNS manifestations in some refractory patients. Intermittent PUVA therapy is warranted in older patients with widespread cutaneous involvement and/or patients with rapidly progressing malignant disease who are unresponsive to more conservative measures. The use of systemic steroid therapy, if any, should be reserved for patients with a more malignant process. In the future, strategies directed at mast cell killing, (possibly through IgE receptors) or focused at cells responsible for regulating mast cell growth should provide a more effective approach in treating patients with proliferative mast cell disorders.

CONCLUSION

Mastocytosis represents a spectrum of disorders that results from an aberrant proliferation of tissue mast cells. The disease may be confined to the skin (Cutaneous Mastocytosis) or may involve multiple organs (Systemic Mastocytosis). Clinical parameters that are useful in differentiating cutaneous from systemic disorders include patient age, symptom complex, and clinical signs. In general, isolated cutaneous disease is most frequently observed in children who have few, if any, associated systemic symptoms and sparse skin lesions. The prognosis for patients with this disorder is usually quite favorable with many becoming disease-free or markedly improved by early adulthood. Patients with adult-onset mastocytosis have approximately an eight-fold greater incidence of systemic disease than children. Severe, mast cell-related systemic symptoms, widespread cutaneous lesions, and evidence of liver, spleen, lymph node, gut and/or bone involvement are hallmarks of systemic involvement. Despite evidence of extracutaneous mast cell proliferation, most patients with this disease remain relatively stable, hence the term, "benign" systemic mastocytosis. Overall, this chronic disease process is associated with a low mortality, but significant morbidity. Of the patients with systemic involvement, a small number will eventually develop a neoplastic disease process (malignant mastocytosis). Over a third of these patients die of a mast cell, myelocytic, or monocytic leukemia. Fortunately, this group represents a very small percentage of patients with mastocytosis.

Treatment of mastocytosis, at present, is supportive with therapy directed at both inhibiting mast cell degranulation and blocking the potential systemic effects of released secretory products. H_1 and H_2 antihistamines in combination with inhibitors of prostaglandin formation appear to offer significant symptomatic relief in a number of patients. The addition of DSCG and/or intermittant PUVA therapy may be warranted in patients who are recalcitrant to more conservative treatment measures. As our knowledge of normal mast cell function expands, new strategies for modifying mediator release will emerge. These approaches should be applicable to the treatment of proliferative mast cell disorders. The most effective therapeutic modalities for patients with mastocytosis, however, will evolve from our future understanding of the basic mechanisms that control the development and growth of the tissue mast cell.

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