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Medical Progress

Mast Cells in Allergic Diseases and Mastocytosis

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Mast cells with their stores of vasoactive and chemotactic mediators are central to the pathogenesis of allergic diseases. The cross-linking of receptor-bound IgE molecules on the surface of mast cells initiates a complex chain of events, including calcium ion influx, phospholipid methylation and turnover and cyclic nucleotide metabolism, ultimately resulting in the release of mediators of immediate hypersensitivity. These mast cell mediators are important in smooth muscle reactivity, in the recruitment of eosinophilic and neutrophilic leukocytes and in the generation of secondary chemical mediators. Histologic evidence of mast cell degranulation, biochemical evidence of mast cell mediators in blood and tissues and clinical evidence of signs and symptoms reproducible by these mediators have strongly supported the crucial role of mast cells in asthma, urticaria, anaphylaxis, rhinitis and mastocytosis. Because of their unique location at host environment interfaces, mast cells may both participate in allergic diseases and promote homeostasis.

In 1877 Paul Ehrlich identified granular cells in connective tissue that stained metachromatically with a variety of pure dyes and that he termed mast cells. In the succeeding 105 years, these cells have been studied extensively with regard to their intracellular structure, granular contents, mode of activation and biochemistry of secretion. The release of granular constituents, the chemical mediators of immediate hypersensitivity, and their subsequent action on surrounding cells and tissues are thought to be major factors in the pathophysiology of asthma, urticaria, rhinitis, anaphylaxis and systemic mastocytosis, and at least a minor component of several other disorders. In this review, "normal" mast cell structure, biochemistry and function will be discussed, and consideration will be given to the contribution of the mast cell to several disease states.

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Physiology and Biochemistry of Mast Cells

Appearance and Location

Mast cells are generally located near small blood vessels, nerves and lymphatics at a concentration in human lung tissue and skin of 1 to 10 million cells per gram.[1] They are found in abundant amounts in loose connective tissue, skin, lymphoid tissue and respiratory epithelium and are found free in bronchial lumina, in bone marrow and in the submucosal layers of the digestive tract.[2-5] Their location at the host-environment interface

ABBREVIATIONS USED IN TEXT

Ca^{++} = calcium
cAMP = cyclic 3′,5′-adenosine monophosphate
Con A = concanavalin A
ECF-A = eosinophil chemotactic factor of anaphylaxis
ETYA = eicosa-5,8,11,14-tetraynoic acid
HETE = hydroxyeicosatetraenoic acid
HHT = 12-*L*-hydroxy-5,8,10-heptadecatrienoic acid
HMW-NCF = high molecular weight neutrophil chemotactic factor
5-HPETE = 5-hydroperoxyeicosatetraenoic acid
PAF = platelet-activating factor
SRS-A = slow-reacting substance of anaphylaxis

allows mast cells to readily participate in allergic and inflammatory reactions. Mast cells are found free in the rat peritoneal cavity, and this ease of access has made rats a common source for obtaining mast cells for experimental purposes.

Mast cells measure 10 to 15 μm in diameter and have an ovoid shape and a ruffled-appearing plasma membrane. They are most notable for the presence of numerous dense metachromatic-staining secretory granules 0.2 to 0.5 μm in diameter, which in humans have a scroll or whorllike appearance. They also possess several types of cellular organelles, including a nucleus, nucleoli, ribosomes, endoplasmic reticulum, mitochondria, Golgi's apparatus and microfilaments. The cells may be stained by single, pure, metachromatic dyes such as toluidine blue, azure A, methyl green or methylene blue.[2,5]

The origin of mast cells is still subject to some speculation, but the likely precursors include primitive mesenchymal cells, fibroblasts, lymphocytes, thymocytes or bone marrow-derived cells. The perivascular, perilymphatic location of mast cells in connective tissue and their relatively fixed position support the theory of an undifferentiated mesenchymal precursor that differentiates locally.[6] That mast cells appear in cultures of tissue specimens of rodent thymus gland suggests that thymocytes or lymphocytes may provide factors helpful in the production of mast cells.[7] The prominence of mast cells in bone marrow in similar numbers to lymphocytes raises the possibility of a bone marrow precursor of mast cells.[8] Furthermore, a select mouse genotype, W/W^V, characterized by anemia and mast cell deficiency, shows a prominent increase in tissue mast cells after bone marrow transplantation.[9] Taken together, these findings do not provide a definitive source for mast cells and imply that they may have more than one type of precursor, depending on their location and the species under consideration.

Mast cells and basophils are similar in that they both possess IgE receptors on their cell surface membranes and both contain histamine. However, basophils are a part of the polymorphonuclear leukocyte series and originate in bone marrow,

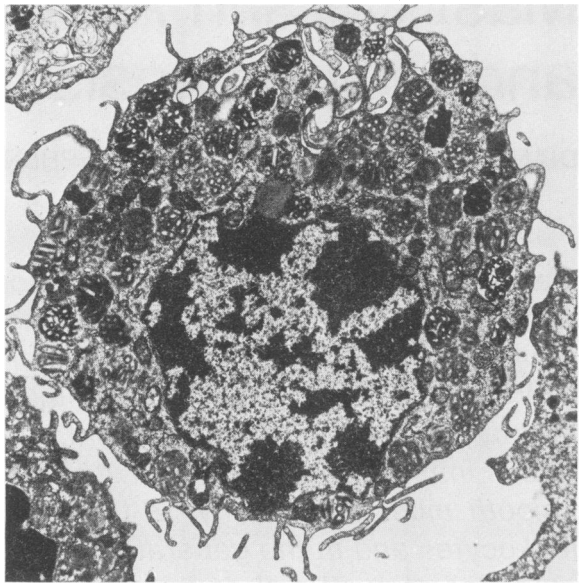

Figure 1.—Human lung mast cell. The cell membrane is reduplicated, the nucleus round and the granules have an intricate subgranular structure. Reproduced with permission from the Journal of Cell Biology (1980; 85:299-312).

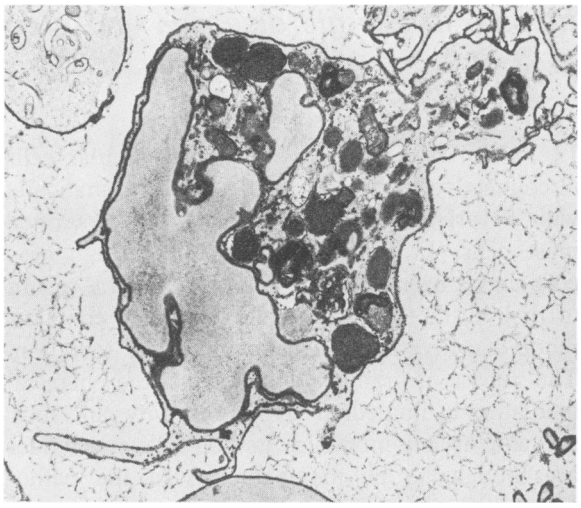

Figure 2.—Human peripheral blood basophil. The cell membrane is relatively smooth with a multilobed nucleus; the cytoplasmic granules possess no structural organization. Reproduced with permission from Laboratory Investigation (1980; 43:126), copyright 1980, U.S./Canadian Division of the International Academy of Pathology.

have no structural organization to their granules, may degranulate one granule at a time and do not contain heparin (Figures 1 and 2).[10] Basophils circulate in the bloodstream and are prominent in tissue in delayed-type hypersensitivity reactions, most notably contact dermatitis.

Granular Contents

The secretory granules of mast cells have been examined most extensively in rat peritoneal mast cells, but some comparative studies of purified human lung mast cells have recently become available. About two thirds of the granule mass is made up of protein, only a portion of which has been specifically characterized. The mast cells possess proteases, notably chymase in rats[11] and a tryptase in humans,[12] and B hexosaminidase,[13] β-glucuronidase[13] and arylsulfatase,[14] suggesting the secretory granules represent modified lysosomes. About a third of the mast cell granule content is macromolecular heparin proteoglycan with a molecular weight of approximately 750,000.[15] The heparin molecule is highly negatively charged, and this property is thought to play an important role in the structural integrity of the granule. Both rat peritoneal and human lung mast cell granules contain the preformed mediator, histamine, bound ionically to the granular matrix, at concentrations of about 25 μg per million cells and 5 μg per million cells, respectively.[16] Rat and mouse mast cells also contain serotonin at concentrations of nearly 2 μg per million cells,[17] and dopamine has been found in small quantities in mast cell granules from some mammals.[4]

Secretagogues and Secretion

Numerous naturally occurring and exogenous agents are able to stimulate mast cells to degranulate and release their stored chemical mediators (Table 1). Perhaps the most pathophysiologically important are the IgE-dependent mechanisms, which account for immediate hypersensitivity reactions. IgE is an immunoglobulin with a molecular weight of approximately 190,000, composed of two light chains and two heavy chains linked covalently by disulfide bonds. The light chains are either k or λ as in other immunoglobulin classes, but the heavy chains are unique in that they contain five complete domains with disulfide bonds between them, and their Fc regions bind avidly to specific receptors on mast cells and basophils.[18] The IgE receptor is comprised of an α-subunit with a molecular weight of 50,000, a part of which binds IgE, and a β-subunit with a molecular weight of 30,000.[19] Rat mast cells have 300,000 such receptors per cell,[20] and when the receptor-bound IgE molecules are cross-linked, mast cell mediator release is initiated.[19] This cross-linking may occur with multivalent antigens, intact antibody to IgE or divalent Fab_2 fragments of anti-IgE, or antibodies to the IgE receptor itself, suggesting that a physical bridging of adjacent receptors is needed to produce mast cell activation and mediator release.[21] In humans the level of circulating IgE in serum correlates well with the number of IgE molecules per basophil and presumably per mast cell.[22] Generally, about 10 percent of IgE receptor sites are occupied, but atopic persons with high serum IgE levels may have up to a 95 percent receptor occupancy rate and, interestingly, often have a larger number of IgE receptors per basophil than normal persons.[22] Whether high levels of IgE cause up-regulation of IgE receptor number by a positive feedback mechanism or whether the IgE receptor number is established at birth and correlates with high IgE levels is not known.

Mast cells may also be degranulated by several non-IgE-dependent agents including the anaphylatoxins, C_{3a} and C_{5a}, concanavalin A (Con A), compound 48/80 and other polyamines, the cal-

TABLE 1.—*Mast Cell Secretagogues That Function In Vivo*

Immunologic mechanisms
IgE-mediated
IgG reagins (?)
Immune complexes
Complement activation (C3a, C5a generation)
Direct activation by receptor cross-linking
Nonimmunologic mechanisms
Direct mast cell degranulation
Drugs
Narcotics
Curare
Succinylcholine
Polymixin B
Radiocontrast media
Complex carbohydrates
Venoms
Irradiation
Arachidonic acid metabolism alteration
Aspirin
Nonsteroidal antiinflammatory agents
Tartrazine (? lipoxygenase pathway)
Complement activation (C3a, C5a generation)
Blood products
Radiocontrast media
Via cleavage by active enzymes

cium ionophore A23187, complex carbohydrates such as dextran, adenosine triphosphate, endotoxins, bee and snake venom proteins and drugs such as narcotics, *d*-tubocurarine, succinylcholine chloride and polymyxin B sulfate.[2,5] These secretagogues act through several different mechanisms, but in general are energy and calcium (Ca^{++}) dependent, result in the uncovering of a serine esterase and cause alterations in membrane lipids.[23]

When a secretagogue acts on the mast cell plasma membrane, usually at specific membrane receptors, subcellular events result in the opening of membrane calcium channels with a brisk calcium influx associated with granule swelling and fusion of granule membranes to each other and to the plasma membrane (Figure 3).[24] This fusion exposes the granular contents to the extracellular environment, where ion exchange with sodium causes the release of mediators that are bound to the granule by low affinity charge interactions such as histamine and eosinophil chemotactic factor.[25] Finally, the mast cell granule may actually be extruded from the cell. The macrophages, neutrophils and eosinophils that accumulate in response to the chemotactic mast cell mediators phagocytose the granules within 24 hours and appear to degrade the granule matrix.[6,26]

Biochemistry of Secretion

A variety of biochemical events take place before mast cell secretion, including changes in cyclic 3′,5′-adenosine monophosphate (cAMP) levels,[27] ionized calcium fluxes,[28] phospholipid methylation,[29] membrane phospholipid turnover,[30] arachidonic acid metabolism,[31] intracellular protein phosphorylation,[32] and the uncovering of a serine esterase (Figure 4).[33] The process requires a source of energy, usually glycolysis, because 2-deoxyglucose in the absence of glucose may suppress mediator release.[34] Although the need for these events is well established, the ordering, relative importance and interrelationship of these pathways remains to be discerned.

cAMP. That cAMP levels fluctuate before and during stimulated mediator release from rat serosal mast cells and mammalian lung fragments is well documented,[27,35] but the precise significance of these changes remains an enigma. The early findings that β-adrenergic agonists and theophylline, both known to increase cellular levels of cAMP, acted synergistically to inhibit IgE-mediated release of histamine and slow-reacting substance of anaphylaxis (SRS-A) from lung fragments, and that β-adrenergic antagonists or α-adrenergic agonists, which decrease cAMP levels, enhanced mediator release, suggested a role of cAMP in the regulation of mast cell secretory events.[36,37] A generalization that became popular was that agents acting to increase cAMP levels inhibit mediator release whereas those that decrease

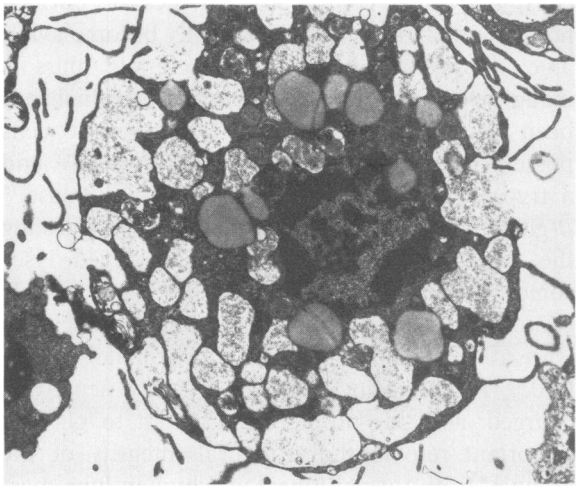

Figure 3.—Human lung mast cell after IgE-dependent activation. Note the granule swelling, loss of subgranular structure, granule fusion and partial granule solubilization. Reproduced with permission from the Journal of Cell Biology (1980; 85:299-312).

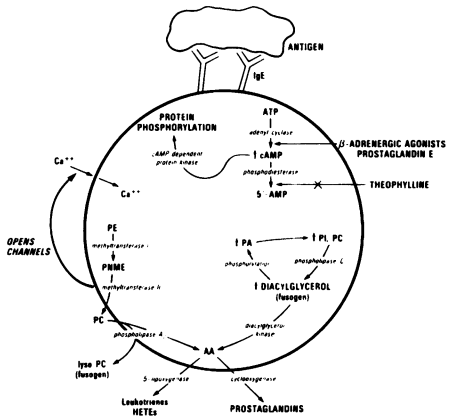

Figure 4.—Simplified schematic diagram of phospholipid methylation, cyclic nucleotide metabolism and phospholipid turnover in a mast cell. Although these cellular events are important in the biochemistry of mast cell activation, their interrelationships have not been defined. Abbreviations: AA = arachidonic acid; ATP = adenosine triphosphate; Ca^{++} = calcium; cAMP = cyclic 3′,5′-adenosine monophosphate; HETE = hydroxyeicosatetraenoic acid; PA = phosphatidic acid; PC = phosphatidylcholine; PE = phosphatidylethanolamine; PI = phosphatidylinositol; PNME = phosphatidyl-*N*-monomethylethanolamine.

cAMP levels augment release. The data, however, were obtained mostly from mixed cell systems.

Studies of purified rat peritoneal mast cells permit analysis of cAMP changes in a single cell type and show varied changes in cAMP levels, depending on the stimulus for activation.[27,38] In most release systems, including those using IgE cell surface receptors, there is a monophasic rise in cAMP levels 5 to 15 seconds after activation that precedes the release of histamine from the mast cells.[27,39] Several investigators have also identified a second monophasic rise in cAMP that occurs after histamine release has peaked, can be suppressed by inhibitors of the cyclooxygenase pathway of arachidonic acid metabolism and is thought to be due to the endogenous mast cell formation of prostaglandin D_2.[39] Contrary to the "increase in cAMP/decrease in mediator release" noted in lung tissue is the finding that prostaglandin D_2 produces a twofold to threefold rise in cAMP but does not inhibit immunologic mediator release from purified rat serosal mast cells.[40] Adenosine[41] and purine-ring modified adenosine analogs also potentiate the early rise in mast cell cAMP associated with activation yet enhance mediator release, whereas ribose-modified adenosine analogs suppress mediator release and decrease adenylate cyclase activity.[42] The crucial factor in cAMP enhancement of mast cell mediator release is the subsequent activation of a cAMP-dependent protein kinase.[43] In IgE-mediated secretion, the initial monophasic cAMP rise is associated with activation of cAMP-dependent protein kinases, whereas cAMP increases caused by prostaglandin D_2 do not affect this intracellular intermediary.[44] In addition to, or as a consequence of, their role in cAMP-dependent protein kinase activation, cyclic nucleotides may also affect secretory granule release by their influence on mast cell microtubule polymerization.[45]

Ionic calcium. Calcium, in a mechanism called stimulus-secretion coupling, is required for several types of secretory cells to extrude their granules.[46] The mast cell intracellular calcium concentration is more than 10,000 times less than the extracellular calcium concentration, and this disparity is maintained by channels for energy-dependent calcium efflux, transport of calcium coupled to sodium transport by an electrochemical gradient and binding of calcium to cytoplasmic structures including glycoproteins and organelles.[47] The importance of calcium in the mast cell mediator-release reaction has been verified in that most secretagogues, with the exception of compound 48/80, which seems to mobilize intracellular calcium stores, require some extracellular calcium to accomplish the secretory process.[2] Calcium uptake occurs immediately before histamine release in rat mast cells stimulated by anti-IgE or the calcium ionophore.[48] The latter is thought to activate mast cells by interacting with cell membrane lipids, forming hydrophobic calcium complexes and thereby facilitating calcium transport down its concentration gradient.[49]

Phospholipid methylation. Some studies show that within 15 seconds after rat mast cells are stimulated with antibodies against IgE receptors and bridging of the IgE receptors occurs, a transient marked increase in ^{3}H-methyl incorporation into membrane lipids takes place, which returns to baseline in 30 seconds.[48] Even in studies that fail to show IgE enhancement of phospholipid methylation, the activation of mast cells by IgE-dependent stimuli in the presence of inhibitors of the methyltransferase reactions is associated with a fall in ongoing methylation, inhibition of the expected calcium influx and inhibition of histamine release.[50] Taken together, these findings suggest that membrane phospholipid methylation is a prerequisite for mast cell mediator release stimulated by anti-IgE. However, degranulating agents that do not cross-link IgE molecules, such as 48/80 and A23187, do not stimulate phospholipid methylation.[29] Biochemical studies of many types of cells including mast cells that methylate phospholipids have shown the presence of two methyltransferase enzymes, the first facing the cytoplasmic side of the membrane and methylating phosphatidylethanolamine to phosphatidyl-*N*-monomethylethanolamine, and the second facing the outer surface of the membrane methylating phosphatidyl-*N*-monomethylethanolamine to phosphatidylcholine.[51] During the presumed translocation of phospholipids from the cytoplasmic side to the outside of membranes by successive methylation, membrane viscosity is likely to be reduced, conceivably opening channels for calcium ion influx. Phospholipase A_2, which catalyzes the hydrolysis of phosphatidylcholine to arachidonic acid and lysophosphatidylcholine, requires calcium for its actions and this calcium influx may help activate the enzyme.[52] Arachidonic acid release from rat leukemic basophils is preceded by phospholipid methylation and augmented by antigenic stimulation,[53] whereas lysophosphatidylcho-

line is a detergentlike fusogen that stimulates mast cell secretion.[54]

Phospholipid turnover. Resting mast cells have been shown to preferentially incorporate $^{32}PO_4$ into membrane phosphatidic acid, phosphatidylinositol and phosphatidylcholine. When mast cells are stimulated with anti-IgE, compound 48/80, Con A or the calcium ionophore A23187, markedly increased labeling of phosphatidic acid occurs within 8 seconds, followed within 30 seconds by labeling of the other two phospholipids.[30] These changes occur before and during the release of mast cell mediators and may be provoked by similar concentrations of the secretagogues required to provoke mediator release. Agents such as theophylline that modulate cAMP metabolism and inhibit histamine release similarly inhibit mast cell phospholipid labeling,[55] and agents that modulate the lipoxygenase pathway of arachidonic acid metabolism such as eicosa-5,8,11,14-tetraynoic acid (ETYA) inhibit both stimulated mast cell mediator release and phospholipid turnover.[56] The parallel changes in phospholipid metabolism and mediator release suggest that mast cell phospholipid metabolism is a central event in the biochemistry of the mast cell secretory process, possibly at least partially through the action of phospholipase C, which produces diacylglycerol from a precursor phospholipid molecule. Levels of diacylglycerol, a potent agent inducing membrane fusion, rise twofold to fourfold during mast cell activation.[57] Phosphorylation of diacylglycerol generates phosphatidic acid, and as this latter molecule is noted to increase within eight seconds of mast cell activation, it is possible that activation of phospholipase C is the earliest step in mast cell mediator release.

Arachidonic acid. Recent studies indicate that arachidonic acid metabolism is required for mast cell mediator release.[31] Arachidonic acid would be made available to the mast cell by either the action of phospholipase A_2 on intact phospholipids or by the sequential action of phospholipase C and diacylglycerol lipase. Arachidonic acid is then metabolized through two major pathways, a 5-lipoxygenase pathway that generates 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and thence the leukotrienes and hydroxyeicosatetraenoic (HETE) acids and a cyclooxygenase pathway resulting in the formation of prostaglandins and thromboxanes.[58] The cyclooxygenase inhibitors, aspirin and indomethacin, in concentrations up to 60 μmol per liter, have no effect on mediator release, suggesting that mast cell cyclooxygenase activity is not necessary for the release process to take place. However, ETYA, an inhibitor of both the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism does inhibit histamine release induced by anti-IgE, Con A or A23187, indicating that patency of the lipoxygenase pathway may be crucial for mast cell secretion.[31] Moreover, 5-HETE and 12-HETE, lipoxygenase products, enhance IgE-mediated secretion.[59]

Resting and activated mast cells seem to metabolize arachidonate somewhat differently. When resting cells are preincubated with free arachidonic acid and subsequently stimulated, mediator release is partially inhibited.[31] This inhibition is blocked by aspirin or indomethacin, implying that resting cells generate a cyclooxygenase product during arachidonic acid metabolism that may render mast cells partially refractory to secretory signals. However, once mast cell secretion is under way, the addition of exogenous arachidonic acid actually enhances mediator release, perhaps due to the generation of lipoxygenase products.[31]

Intracellular protein phosphorylation. Rat mast cells stimulated with 48/80 or A23187 within ten seconds phosphorylate three mast cell proteins with molecular weights of 68,000, 59,000 and 42,000 in a calcium-dependent process. A fourth protein of molecular weight 78,000 is phosphorylated 30 to 60 seconds after 48/80 (but not A23187) stimulation when secretion is well under way.[32] When mast cells were prelabeled with ^{32}P and incubated with sodium cromoglycate, a drug that inhibits mast cell mediator release by unknown mechanisms, only the phosphorylation of the 78,000 molecular weight protein was enhanced, again relatively late in the course of the response.[60] From these results it has been postulated that the early protein phosphorylation seen after mast cell activation may be related to the exocytotic secretory response, whereas the late phosphorylation of the 78,000 molecular weight protein might be a component of the mechanism of calcium-gate closure. Other investigators recently identified an early phosphorylation of the IgE receptor of rat mast cells within 15 seconds after stimulation by A23187 and suggest the possibility that this step may be important in transmitting extracellular signals into the cell.[61] These phosphorylation steps presumably are dependent on adenylate cyclase generation of cAMP and

activation of the cAMP-dependent protein kinases (see above).

Serine esterase. The need for uncovering of a serine esterase for mast cell secretion to occur is suggested by the fact that isoflurophate, an irreversible serine esterase inhibitor, prevents antigen-induced mediator release from rat serosal mast cells and human lung fragments.[33,62] If isoflurophate is added to unstimulated cells but removed before activation, no effect on mediator release is seen, suggesting that the esterase is protected in resting cells. There is no direct evidence other than these studies that these organophosphorus inhibitors are acting only on the serine esterase and do not interact with mast cells in some other way to inhibit the secretory process.

Although it is not possible at the present time to be certain of order and interrelationship of these various biochemical processes in mast cell activation, it is tempting to speculate that the initial bridging of IgE molecules activates two basic but related processes, namely phospholipid metabolism and cAMP generation. The metabolism of phospholipids would be expected to generate fusogenic substances which enables membrane fusion, to liberate arachidonic acid, which enables enhanced mediator release via 5-HETE and 12-HETE, and to alter membrane fluidity, which permits adenylate-cyclase coupling to protein kinase and perhaps enhances Ca^{++} ion flux. Concurrently, adenylate-cyclase activation and generation of cAMP would be translated by cAMP-

TABLE 2.—*Vasoactive Smooth Muscle Reactive Mediators*

Mediator and Source	*Preformed or Generated*	*Function*	*Therapeutic Inhibitor*
Histamine (mast cell basophil)	Preformed	H_1: Contract smooth muscle Increase vascular permeability Increase cGMP Generate prostaglandins	Classical antihistamine
		H_2: Increase vascular permeability Increase gastric acid secretion Increase cAMP Stimulate suppressor T lymphocytes	Cimetidine
Serotonin (platelet)	Preformed	Increase vascular permeability Contract smooth muscle Released by PAF action	Hydroxyzine Cyproheptadine
Arachidonic acid metabolites			
Leukotrienes C_4,D_4,E_4 (SRS-A) (neutrophils macrophages mast cells ?)	Generated	Constrict smooth muscle Increase vascular permeability Decrease peripheral blood flow (C_4) Vasodepressors Synergistic with histamine Generate prostaglandins	Glucocorticoids may prevent generation
Prostaglandins	Generated		Aspirin and nonsteroidal antiinflammatory agents block generation
D_2 (mast cells)		Increase cAMP level Contract smooth muscle Increase vascular permeability	
E_2, $F_{2\alpha}$, I_2 (prostacyclin), Thromboxane A_2 (many cell types)		Relax smooth muscle Increase cAMP level, contract smooth muscle Decrease cAMP level Contract smooth muscle Increase cAMP level Inhibit platelet aggregation Contract smooth muscle Induce platelet aggregation	
Platelet-activating factor (mast cells ? macrophages neutrophils)	Generated	Aggregate platelets Release platelet amines Sequester platelets in tissue Induce vascular permeability Vasodepressor Vasoconstriction Bronchoconstriction	None

cGMP = cyclic guanosine monophosphate; cAMP = cyclic 3′,5′-adenosine monophosphate; PAF = platelet-activating factor; SRS-A = slow-reacting substance of anaphylaxis.

dependent protein kinase activation into the phosphorylation of key proteins, some of which may regulate calcium influx, intracellular translocation of granules to the cell surface and transport of ions into the granules, resulting in granule solubility and mediator discharge.

Mediators

The activation and degranulation of mast cells causes the release of preformed, granule-associated (primary) mediators and the generation and release of unstored (secondary) mediators (Table 2). Table 2 denotes these mediators in terms of their functions, which include smooth muscle reactivity, chemotactic potential and enzymatic activity, and structural properties. The mediators have been best defined using rat mast cells, but in most instances human mast cells have proved similar.

Smooth muscle reactive mediators. Histamine, the decarboxylation product of histidine, is ionically bound to the proteoglycan-protein backbones of mast cell and basophil granules.[63] The sole mediator in this functional class preformed in human mast cells, it is displaced by sodium exchange in the extracellular fluid.[25] Histamine is catabolized by either oxidative deamination (histaminase) or by combined demethylation and oxidative deamination (histamine *N*-methyltransferase plus monoamine oxidase). The effects of histamine are expressed as constriction of smooth muscle and an increase in the distance between endothelial cells of venules, thereby increasing the potential for transudation of serum and for extravasation of leukocytes. The biologic activities of histamine follow its interaction with two specific classes of receptors on target cells. H_1 receptors predominate in skin and smooth muscle and are inhibited by classic antihistamines, whereas H_2 receptors are selectively blocked by burimamide, metiamide and cimetidine.[64] Pulmonary bronchoconstriction, vasodilation and increased cyclic guanosine monophosphate (cGMP) are H_1 receptor effects, whereas H_2 receptor effects include elevations in cAMP,[65] activation of human suppressor T lymphocytes[66] and inhibition of IgE-mediated basophil histamine release. The wheal-and-flare response to histamine in skin is due to a combined effect on H_1 and H_2 receptors.[67]

Slow-reacting substance of anaphylaxis is comprised of closely related products of the 5-lipoxygenase pathway of arachidonic acid metabolism termed leukotrienes C, D and E.[68,69] These compounds differ only in the amino acid constituents of a glutathione side chain. All are potent constrictors of peripheral airways smooth muscle; leukotriene D is the most active in this regard, and whereas both C and D are vasodepressors, leukotriene C constricts and D relaxes cutaneous vasculature.[69,70] Decreasing amounts of SRS-A are generated by increasingly pure human mast cell preparations, suggesting alternative sources of this class of mediator.[1] Such a source may be a human macrophage.[71]

Other products of arachidonic acid oxidation. Arachidonic acid mobilized from cell membrane phospholipids may be converted, via a cyclooxygenase-dependent pathway, to prostaglandins and thromboxanes, or by a 5-lipoxygenase enzyme to various hydroxyeicosatetraenoic acids and related compounds. The cyclooxygenase product prostaglandin D_2 has been generated by IgE-dependent activation of rat and human mast cells.[72] Other metabolites, including prostaglandins F_2 and E_2, have been identified after IgE-dependent activation of chopped human lung.[35] Animal and human smooth muscle is constricted by prostaglandins $F_{2\alpha}$ and D_2, thromboxane A_2, and both cyclic prostaglandin endoperoxides, G_2 and H_2, whereas prostacyclin (prostaglandin I_2) and prostaglandin E_2 relax smooth muscle. Following antigen challenge of sensitized guinea pig lung tissue, bronchoconstrictor metabolites of arachidonic acid predominate. In the skin, prostaglandin E causes a prolonged erythema.

Platelet-activating factor (PAF). [1-0-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine] is a unique phospholipid generated from rabbit but not human basophils by IgE-dependent mechanisms.[73] Its human source appears to be neutrophils and perhaps mast cells. Synthetic PAF is capable of inducing aggregation of human platelets and secretion of their serotonin. When injected into human skin, PAF causes local edema and erythema.[74] In animals PAF induces sequestration of platelets in lung tissue or skin and is a potent vasodepressor. Removal of platelets does not abrogate these effects of PAF.[75] In addition, in a platelet-dependent reaction PAF causes bronchoconstriction in animals.[75,76]

Serotonin is contained in human platelets, rather than mast cells or basophils, and may be released by the action of PAF. Whereas serotonin is capable of inducing vascular permeability in the

skin of rodents[77] and of contracting gastrointestinal smooth muscle,[78] it is ineffective as a constrictor of airways smooth muscle.

Chemotactic Mediators

Eosinophil chemotactic factor of anaphylaxis (ECF-A), the first mast cell-derived chemotactic factor described,[79] has been identified in anaphylactic supernatants of human lung mast cells, where it appears to be preformed,[1] and is released into the circulation of patients with experimentally induced urticaria (Table 3).[80,81] An acidic family of small peptides, ECF-A has been extracted from whole human lung tissue and structurally characterized from this source as two tetrapeptides with the sequence Val or Ala-Gly-Ser-Glu (valine or alanine-glycine-serine-glutamine).[82] This factor is preferentially chemotactic for eosinophils and deactivates them from further migration. A similar factor of greater hydrophobicity has been isolated from the serum of patients after experimental induction of cold urticaria (Figure 5).[83]

Intermediate molecular weight eosinophil chemotactic peptides. In addition to the low molecular weight, acidic ECF-A peptides, human lung and rat mast cells contain preformed and immunologically releasable chemotactic factors of molecular weight 1,500 to 3,000, with specificity for eosinophil polymorphonuclear leukocytes.[84,85] Factors of similar molecular weight and chemotactic specificity have been identified in the circulation of

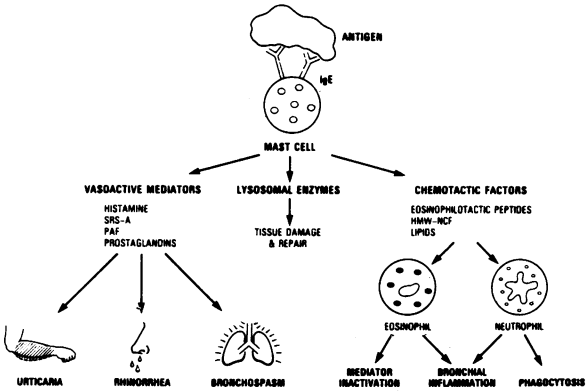

Figure 5.—Mast cell activation culminates in the release of three classes of chemical mediators that are partially responsiible both for allergic disease symptoms and the restoration of homeostasis. Abbreviations: HMW-NCF = high molecular weight neutrophil chemotactic factor; PAF = platelet-activating factor; SRS-A = slow-reacting substance of anaphylaxis.

TABLE 3.—*Chemotactic Mediators*

Mediator and Source	*Preformed or Generated*	*Function*	*Therapeutic Inhibitor*
Eosinophil chemotactic factor of anaphylaxis (mast cells)	Preformed	Attract and deactivate eosinophils Increase eosinophil C_{3b} receptors	Glucocorticoids block effect Xanthines and β-agonists inhibit release
Eosinophil chemotactic factor oligopeptides (mast cells)	Preformed	Attract and deactivate eosinophils and mononuclear leukocytes (more acidic peptide)	Glucocorticoids block effect Xanthines and β-agents inhibit release
Neutrophil chemotactic factor (mast cells ?)	? Preformed	Attract and deactivate neutrophils	Glucocorticoids block effect Xanthines, β-agents and cromolyn inhibit release
Histamine	Preformed	H_1: Activation of directed and random migration of eosinophils H_2: Inhibition of directed and random migration of eosinophils and neutrophils	Classical antihistamine Cimetidine
Arachidonic acid metabolites			
Cyclooxygenase products HHT (many cell types)	Generated	Activation of directed and random migration of neutrophils and eosinophils	Aspirin and nonsteroidal antiinflammatory agents prevent generation
Lipoxygenase products HETE (many cell types)	Generated	Augmented random and directed migration of neutrophils and eosinophils	? Glucocorticoids prevent generation
Leukotriene B_4		Augmented random and directed migration of neutrophils and eosinophils	? Glucocorticoids prevent generation

HHT = 12-*L*-hydroxy-5,8,10-heptadecatrienoic acid, HETE = hydroxyeicosatetraenoic acid.

patients following experimental induction of urticaria.[83]

High molecular weight neutrophil chemotactic factor (HMW-NCF). HMW-NCF has been described in human lung fragments and the sera of patients with urticaria[80,86] or asthma[82,87] following appropriate challenge. It has been characterterized as a 750,000-dalton neutral protein that attracts and deactivates neutrophils. HMW-NCF is a sensitive marker for mast cell activation as it is present in sera of allergic asthmatic patients following challenge with doses of antigen insufficient to induce bronchospasm.

Lipid chemotactic factors. Chemotactic factors with specificity for both neutrophilic and eosinophilic polymorphonuclear leukocytes can be generated by lipoxygenase and cyclooxygenase-dependent pathways of arachidonic acid metabolism. The former pathway generates the HETE compounds (5,8,10,11- or 12-*L*-hydroxy-5,8,11,14-eicosatetraenoic acid) and leukotriene B_4 whereas the latter produces 12-*L*-hydroxy-5,8,10-heptadecatrienoic acid (HHT). These molecules have not yet been shown to be generated in immediate hypersensitivity reactions or by human mast cells. HETE molecules have an ECF-A-like spectrum of activity but enhance random migration and are less potent deactivators.[88] HHT has similar actions on neutrophils.[89] Leukotriene B appears to be a potent chemotactic and chemokinetic factor acting primarily on neutrophils.[90]

Other chemotactic factors. Activities directed toward lymphocytes have been reported to be observable in rat mast cells, whereas a chemotactic factor for mononuclear leukocytes is released into the circulation in cold urticaria.[83]

Granule-Associated Enzymes

Tryptase. A preformed tryptic protease termed tryptase is released following antigen challenge of IgE-sensitized human mast cells (Table 4).[91] This enzyme may cleave kininogen to yield bradykinin and to activate the Hageman factor..[92] The released kinins may contract smooth muscle, increase vascular permeability and induce pain. Activation of the Hageman factor could recruit the clotting, fibrinolytic and complement cascades. A potent chymotryptic enzyme termed chymase is present in rat mast cells, but is not found in human mast cells.

Other lysosomal enzymes. Myeloperoxidase, superoxide dismutase, arylsulfatase A and B, β-glucuronidase, hexosaminidases and aminopeptidase have been identified in isolated human or rat mast cells.[93] The function of these lysosomal enzymes remains speculative.

Structural Proteoglycans

Heparin, a sulfated, metachromatic mucopolysaccharide has been identified in mast cells from human lung.[94] Human heparin has a molecular weight of 60,000 and is comprised of a protein

TABLE 4.—*Enzymes and Proteoglycans*

Mediator and Source	*Preformed or Generated*	*Function*	*Therapeutic Inhibitor*
Tryptase (mast cell)	Preformed	Generate bradykinin Activate Hageman factor Proteolysis Degrade ground substance (?)	None
Arylsulfatase A (mast cell)	Preformed	Cleave sulfate esters Degrade ground substance (?)	None
Hexosaminidase (mast cell)	Preformed	Cleave hexosamines Degrade ground substance (?)	None
β-Glucuronidase (mast cell)	Preformed	Cleave glucuronide residues	None
Superoxide dismutase (mast cell)	Preformed	Cleave oxygen radicals	None
Myeloperoxidase	Preformed	Cleave hydrogen peroxide	None
Heparin (mast cell)	Preformed	Anticoagulation Bind to antithrombin III and platelet factor IV Inhibit complement activation Bind other preformed mediators	Protamine
Chondroitin 4 and 6 sulfates (basophils)	Preformed	Bind basophil mediators Bind to platelet factor IV	None

core to which are attached glycosaminoglycan side chains. Human heparin interacts with human antithrombin III to accelerate anticoagulation and may inhibit complement activation at several steps.[95] Basophilic leukocytes contain chondroitin sulfates rather than heparin as their granule-associated proteoglycan.

Mediator Interactions

The mediators of immediate hypersensitivity have been isolated, identified and characterized as individual factors, whereas immediate hypersensitivity syndromes reflect their combined interactions. Given the number of mediators, most have yet to be fully purified and there is little understanding of appropriate ratios of mediators generated or released in vivo.

The effects of histamine and SRS-A on smooth muscle are synergistic in vitro, and both histamine and SRS-A are known to cause prostaglandin generation. In addition, histamine may potentiate or inhibit ECF-A-induced eosinophil chemotaxis, depending on the ratio of individual mediators. These simple interactions suggest the many possible and potentially critical biological interactions yet to be elucidated. For example, the generation of PAF and SRS-A from neutrophils and mononuclear leukocytes suggests an important role for chemotactic mediators in regulating the availability of other crucial mediator-generating cells.

The Role of Mast Cells and Their Mediators in Tissue

The most direct evidence regarding the potential role of mast cells in inflammation has been generated in studies of human skin.[96,97] Using antibodies to IgE or antigen challenge of skin sites passively sensitized with pure IgE, it has been possible to discern several pathophysiologic consequences of mast cell activation. The initial event following mast cell activation is a pruritic wheal-and-flare reaction beginning in minutes and peaking 30 to 60 minutes after challenge. This reaction is characterized histologically by mast cell degranulation, endothelial activation and edema formation. After several hours the challenged site may become tender, erythematous and diffusely swollen. A biopsy specimen at this stage reveals the findings noted in the initial reaction, plus infiltration of neutrophils, eosinophils, basophils, lymphocytes and mononuclear leukocytes.[96,97] Often there are accompanying hemorrhage and fibrinoid vessel necrosis sufficient to warrant a diagnosis of necrotizing vasculitis.[96] These properties are certainly relevant to the allergic diseases, as discussed below, but may also be of great importance in homeostatic regulation at the host-environment interface. This latter speculation is strengthened by the fact that mast cells are found predominantly at this interface. Their homeostatic role may be related to removal of noxious particles, parasites and bacteria and in the regulation of the microvasculature.

Clinical Introduction

Although the mechanisms of mast cell mediator release and the structure and function of chemical mediators have been studied extensively in vitro, the role of mast cells in clinical disease is not as well defined. Because of their large number of IgE receptors and stores of chemical mediators of immediate hypersensitivity, one would expect mast cells to be crucial to the pathophysiology of allergic disease (Figure 5). The perception of the role of mast cells in disease has been based on histologic analysis showing mast cell degranulation, the identification of known mast cell products in biologic specimens or by the occurrence of signs and symptoms reproducible by specific mast cell mediators (Table 5). The following sections will attempt to clarify what is known about mast cells and their mediators in the pathogenesis of asthma, urticaria, angioedema, anaphylaxis and mastocytosis.

Asthma

Several types of pathologic and physiologic evidence show the importance of mast cells and their mediators in allergic asthmatic reactions. Mast cells can be found free in human bronchial lumina, in mucosa and submucosa of normal respiratory epithelium and in pulmonary secretions.[2,5] The density of mast cells increases as the airways become smaller, from 250 to 500 cells per cu mm in the trachea and bronchi and up to 1,000 cells per cu mm in more peripheral bronchioles.[98] In autopsies of patients with acute asthmatic attacks, mucous plugging, epithelial sloughing, smooth muscle hypertrophy, eosinophilia and occasional mucous gland hypertrophy are seen,[99] and the number of mast cells is diminished when compared with that of normal persons, presumably due to their degranulation.[100] This impression is supported by the finding that there are more degranulated mast cells in lung specimens

TABLE 5.—*Evidence Suggesting Mast Cell Participation in Disease*

Histologic evidence
Changes in mast cell numbers in tissues
Demonstration of mast cell degranulation
Presence of cells possibly recruited by mast cell mediators (eg, eosinophils, neutrophils)
Endothelial activation and disconnections
Biochemical evidence
Elevated levels of mediators in blood or secretions
Identification of mediators in tissue specimens
Specific IgE or antigen in blood or tissue
Clinical evidence
Signs and symptoms reproducible by mast cell mediators
Wheal-and-flare skin reaction
Pruritus
Bronchospasm
Rhinorrhea
Hypotension
Diarrhea
Pharmacologic agents that inhibit mast cell mediator release or mediator effects reduce symptoms
Antihistamines
Theophylline
Sodium cromolyn
β-Adrenergic agonists (?)

from persons with active asthma than in persons without asthma or with inactive asthma.[101] In sensitized dogs, challenge with appropriate antigens causes a decrease in airway mast cell numbers and in the content of lung histamine, whereas plasma histamine levels rise,[102] suggesting acute mast cell degranulation and release of mediators of immediate hypersensitivity. Humans suffering from acute antigen-induced asthma also have shown an augmentation of plasma histamine[103] and neutrophil and eosinophil chemotactic factor[87] levels from baseline, and patients with skin-test positive asthma have higher levels of histamine in their sputum than normal persons.[104]

The role of mast cells in nonallergic asthma is, however, less well defined. One hindrance to the elucidation of this role has been the difficulty in assessing small changes in plasma histamine. Fluorometric analyses are probably without validity in biologic fluid and only recently have adaptations of enzymatic histamine analysis proved sufficiently sensitive. With this technique, it has recently been shown that patients with exercise-induced asthma[105] and some patients inhaling methacholine[103] have rises in plasma histamine levels. Moreover, diurnal alterations in pulmonary function characteristic of some asthmatic patients parallel circadian changes in plasma histamine levels. Aspirin-induced asthma and cold-air induced bronchospasm, however, do not appear to be associated with appreciable mast cell mediator release.

Aside from direct measurements and observations, the prominent role of mast cells in asthma also has been implied by the pathophysiologic effects of its chemical mediators. Histamine constricts airway smooth muscle both by a direct local effect on irritant receptors[106] and by a reflex vagal pathway that can be blocked by atropine.[107] Histamine also increases the permeability of pulmonary venules, facilitating vascular protein leakage and edema formation.[108] Leukotrienes C, D and E (SRS-A) are potent bronchial smooth muscle constrictors preferentially acting on peripheral airway smooth muscle and also inducing edema formation.[109] These agents are 10-fold to 100-fold more potent on a weight basis than histamine in inducing bronchoconstriction. Prostaglandin D_2, formed by the metabolism of arachidonic acid via the cyclooxygenase pathway in mast cells, is another agent that constricts bronchial smooth muscle.[110] To date, however, there is no direct evidence that leukotrienes or prostaglandins are important mediators in human asthma. Platelet-activating factor, whose precise cellular source is unknown, appears during IgE-mediated reactions in which mast cells and basophils participate.[73] PAF induces bronchoconstriction in a platelet-dependent reaction that is associated with pulmonary platelet sequestration.[75,76] Such platelet sequestration and activation caused by PAF provides a source of platelet-derived mediators locally in lung tissue.

Finally, the effect of some pharmacologic agents in both ameliorating asthma and inhibiting mast cell activation suggests that mast cells are vital to asthmatic reactions. Theophylline, β-adrenergic agonists and sodium cromoglycate all inhibit histamine release from stimulated mast cells and decrease airways resistance in asthmatic patients, and are useful agents in the treatment of asthma.

The pathophysiology of the late phase of antigen-induced bronchospasm and the genesis of the bronchial hyperreactivity that is characteristic of asthma may also be due to mast cells. Late-phase reactions to allergen inhalation are seen as decreased pulmonary function occurring four to eight hours after antigen inhalation. Initially attributed to IgG immune complex reactions, these late reactions have been shown in skin to be clearly IgE mast cell mediated and associated with leukocyte infiltration and blood vessel damage.[97] As both early- and late-phase asthma are prevented

by pretreatment of patients with disodium cromoglycate,[111] whereas only the late phase is prevented by glucocorticoids,[112] it is reasonable to conclude that a mast cell-dependent inflammatory reaction is central to late-phase asthma. Of interest is that bronchoreactivity to histamine is altered in patients experiencing late-phase asthma but not in those in whom only the early phase can be identified.[113] It is presumed, therefore, that mast cell chemotactic factors and enzymes (see above) create an inflammatory substrate on which the chronicity of asthma may develop.

Urticaria and Angioedema

Urticaria is a raised, erythematous, blanching and pruritic cutaneous lesion similar to the wheal-and-flare reaction produced when histamine is injected into the skin. It may be IgE-mediated or associated with complement activation, immune complex reactions or caused by agents that induce mast cell degranulation directly and by agents that alter arachidonic acid metabolism.[114] Angioedema, a frequent companion of urticaria, is characterized by deep swellings that most commonly affect the face, lips, tongue, pharynx and extremities, but may occur in any area of the body. The disorders exhibit similar pathologic alterations in skin biopsy specimens, which reveal dilated microvasculature in the superficial and deep dermis, swollen collagen fibers and flattened rete pegs with occasional perivascular cellular infiltrates.[115,116] Mast cells are prominent in the normal dermis near vessels, nerves and hair follicles, with a density of approximately 7,000 cells per cu mm.[117] In urticaria, the mast cell density is probably normal, though some reports suggest an increase in mast cell numbers and the presence of mast cells in the epidermis.[118] Light and electron microscopy of urticated skin shows degranulating mast cells, evidence of endothelial activation and endothelial disconnections.[119] These latter findings are consistent with the known effects of histamine on the cutaneous vasculature.

Because they can easily be reproduced by specific stimuli, two types of urticaria, cold urticaria and cholinergic urticaria, have been studied extensively for the release of mast cell mediators into the circulation. Clinically, in patients with cold urticaria when exposed to cold air, cold water or ice, pain develops in the affected areas and on rewarming tingling, pruritus and whealing develop. Persons with this disorder may have oropharyngeal edema after swallowing cold fluids.[120] Many patients with idiopathic cold urticaria have IgE capable of transferring cold responsiveness to normal skin.[120] In patients with cold urticaria challenged by immersion of one arm in an ice bath for three minutes prominent elevations in serum histamine concentrations develop and there are increased levels of three eosinophil chemotactic factors[80] and a single high molecular weight neutrophil chemotactic factor[86] in venous blood draining the urticated site. A biopsy specimen from these urticated areas shows mast cell degranulation.[121]

Cholinergic urticaria, a non-IgE-mediated disorder, may be provoked by a rise in the core body temperature due to pyrexia, warm baths or exercise. Cholinomimetic preparations injected intradermally produce a wheal-and-flare response in a third of these patients, and may induce smaller satellite lesions surrounding the original wheal, felt to be pathognomonic for cholinergic urticaria.[114] In nearly all such patients, this type of urticaria develops after warm baths or exercise and plasma histamine levels become elevated, as well as those of neutrophil and eosinophil chemotactic factors after experimental reproduction of their attacks.[122] Similarly, in a large group of patients with various forms of physical urticaria and idiopathic urticaria, suction blisters of lesional skin had increased content of histamine as compared with similar blisters on uninvolved skin.[123] Thus, release of mast cell mediators can be shown in both IgE- and non-IgE-mediated urticaria.

The cutaneous manifestations of histamine include an area of central erythema and edema formation (the wheal) with a surrounding flare or flush.[124] As little as femtomolar concentrations of histamine in the skin have been shown to cause pain and pruritus,[125] presumably acting through small nerve endings. Antihistamines, especially the H_1 receptor antagonists, have long been the mainstay of treatment of urticaria, though H_2 antihistamines may provide some added benefit. Other secondary mast cell mediators, including PAF, prostaglandins D_2 and E_2, leukotriene D and perhaps bradykinin, also increase vascular permeability and may produce wheal-and-flare responses when injected intradermally,[3] but their role in the development of urticaria is unknown.

Anaphylaxis

Systemic anaphylaxis is a life-threatening reaction often mediated by IgE and produced by

the actions of several chemical mediators on cardiovascular, cutaneous, respiratory and gastrointestinal target tissues. In IgE-mediated anaphylaxis, the reaction requires an initial exposure to an antigen, a latent sensitization period and subsequent reexposure to the antigen. Other anaphylactic reactions (sometimes called anaphylactoid) due to immune complexes, complement activation, direct mast cell degranulation and aspirinlike agents are clinically identical to anaphylaxis but occur on a nonimmunologic basis. Anaphylaxis is characterized by its effects on the noted target tissues and occurs as urticaria or angioedema, hypotension, cardiac arrhythmias, upper and lower respiratory tract obstruction, abdominal pain, vomiting and diarrhea, all of which may occur singly or in combination. Penicillin medications and hymenoptera stings are the most common causes of IgE-mediated anaphylaxis today, though horse serum provided most of the early examples. Radiocontrast media, aspirin and blood products provide most examples of non-IgE-mediated forms.

Clinical signs and symptoms usually develop within 30 minutes after exposure to the eliciting stimulus. A patient may notice first a tingling in the mouth or face, followed by warmth, flushing, pruritus and throat and chest tightness.[126] Bronchospasm, laryngeal edema, hypotension, vasomotor collapse and cardiac arrhythmias may ensue. Pathological findings correlate well with the clinical picture, such as pulmonary hyperinflation and edema, laryngeal edema, intraalveolar hemorrhage, bronchial hypersecretion, eosinophils in the bronchial walls and visceral congestion, though in some instances no pathological abnormalities have been identified.[126]

Although few studies of patients with active anaphylaxis have been done to identify the causative mediators, several mast cell and basophil-associated agents have been implicated in the pathophysiology of anaphylactic reactions. Histamine produces urticaria, angioedema, vasodilatation, hypotension, increased vascular permeability, vomiting and tenesmus[127] and is probably central in the pathogenesis of anaphylaxis. Leukotrienes are potent bronchial smooth muscle constrictors, some of which also increase vascular permeability and reduce pulmonary compliance in vivo.[70] Platelet-activating factor, another mediator generated by IgE-dependent mechanisms, causes local aggregation and degranulation of platelets and profound hypotension in animal models of anaphylaxis.[128] Eosinophil chemotactic factors may explain the tissue eosinophilia observed in anaphylaxis.

Rhinitis

Histologically a normal nasal biopsy specimen shows ciliated pseudostratified columnar epithelium, an underlying basement membrane, lamina propria, perichondrium and cartilage.[129] Small numbers of mast cells are present in the lamina propria near blood vessels and in loose connective tissue. Significantly, nasal mast cells are more abundant in nasal scrapings from persons with chronic allergic rhinopathy or nasal polyps[130]; however, there is little direct evidence proving the role of these cells in allergic or nonallergic rhinitis. Allergic persons do show elevated IgE levels in the nasal mucosa associated with hypereosinophilic nasal secretions.[131]

Evidence obtained in vitro suggests that in vivo when IgE bound to mast cells or basophils in the nasal mucosa interacts with extrinsic antigen, degranulation occurs followed by release of mediators of immediate hypersensitivity that act on nasal effector organs, namely blood vessels, goblet cells and mucosal glands. Clinical interaction with antigen results in swollen mucous membranes, nasal obstruction, hypersecretion, sneezing and itching, the classic symptoms of allergic rhinitis. That mast cell mediators are relevant to allergic rhinitis is attested to by the findings that histamine directly applied to the nasal mucosa produces an immediate profound rhinorrhea, dilating nasal blood vessels via H_1 receptors and increasing capillary permeability.[132] The presence of eosinophils suggests that ECF-A secretion from mast cells may be an important factor. The role of SRS-A and PAF in rhinitis is not known, and whether prostaglandins, which may either dilate or constrict nasal capillaries, have any clinical significance is uncertain. Essentially nothing is known about the role of mast cells in non-IgE-mediated rhinitis.

Many systemic or topical agents have been used to help ameliorate the symptoms of allergic rhinitis, with variable efficacy. Antihistamines administered orally are most often used to treat rhinorrhea and pruritus and are generally beneficial, especially in mild disease. Topically given disodium cromoglycate, perhaps by its effects on mast cell mediator release, has been useful in some

patients,[133] especially in those with eosinophilia on nasal smears.

Mastocytosis

Mastocytosis is an abnormal accumulation of mast cells in various tissues that can take several forms. The cutaneous form may be localized to a discrete area, often called a mastocytoma, or occur as a generalized involvement of the skin, urticaria pigmentosa.[134] Systemic mastocytosis almost always involves the skin, but mast cells may proliferate as well in liver, spleen, lymph nodes, the gastrointestinal tract, bone marrow, thymus and bone.[134] A third category of mastocytosis is mast cell leukemia, a very rare malignant form of mast cell proliferation.

Any type of mastocytosis is rare, occurring in 1 in 2,500 patients seen in a dermatologic clinic in one series.[135] The disease occurs most often in whites and usually has no identifiable hereditary component, though some family studies have described an autosomal dominant pattern of inheritance.[136] The purely cutaneous forms are most often seen in childhood and may wane with age, but 15 percent to 30 percent of those with skin involvement also have the systemic form of the disease, and this form predominates in adulthood.

The skin lesions of mastocytosis are classically reddish brown papules and plaques, primarily of the trunk, that urticate with contact (Darier's sign). Biopsy specimens of the skin lesions show large numbers of mast cells,[117] especially in dermis, generally clumped near small blood vessels and nerves. The concentration of histamine in the skin of patients with urticaria pigmentosa is five to ten times normal levels.[137]

The clinical features of mastocytosis may be attributed either to mast cell infiltration of tissues or to the pharmacologic effects of mast cell mediators on various organs. Mast cell infiltration of the liver or spleen may cause hepatomegaly or splenomegaly,[138] and rarely lymphadenopathy may result from the physical presence of mast cells in lymph nodes.[139] When mast cell infiltration of the bone marrow is pronounced, anemia or leukopenia may result, and mast cells may be present in the peripheral blood. The malignant form of this disorder, mast cell leukemia, said to occur in up to 4 percent of those with mastocytosis, but which certainly is much less common, is a rapidly fatal disease with total peripheral mast cell counts in the blood of 60,000 to 70,000 per cu mm.[139]

Mast cell proliferation in bone, best identified by technetium Tc 99m bone scanning, may show osteoporotic or osteosclerotic changes radiographically, and some patients with bony involvement have bone pain. Histamine is the predominant preformed mast cell mediator that produces clinical symptoms in patients with mastocytosis. Its release in the skin occurs as dermatographia, pruritus, urticaria and flushing.[124] The latter symptoms and associated hypotension may be due not only to histamine, but also to the mast cell metabolite of arachidonic acid, prostaglandin D_2. Although the symptoms of mastocytosis generally occur without clear-cut precipitating events, the ingestion of alcoholic beverages may trigger acute symptoms,[140] presumably through a histamine-release phenomenon. Such acute episodes may at times be confused with anaphylaxis. The gastrointestinal manifestations of histamine excess include nausea,[141] diarrhea, steatorrhea, malabsorption, peptic ulcer disease and gastrointestinal bleeding,[142] which may be aggravated by release of heparin from mast cell granules.[143] When mast cell proliferation in the nose is prominent, histamine may contribute to a pronounced rhinorrhea.[139] Other symptoms thought to be due to high circulating levels of histamine include palpitations, tachycardia, malaise, headache, cognitive disorganization and bronchospasm.[139] These signs and symptoms may be confused with those of the carcinoid syndrome but, as seen in Table 6, the different mediators produce different clinical and laboratory findings.

Hematologic findings may relate to other mast cell constituents. Mast cells contain factors chemotactic for eosinophils that may contribute to the peripheral blood eosinophilia seen in some patients with mastocytosis.[144] A prolonged partial thromboplastin time in other patients with mastocytosis has been attributed to the release of heparin from mast cell granules.[139] Some patients may also have hypocholesterolemia, possibly due to heparin's effect on cholesterol metabolism.[144]

In the past, the mainstay of treatment for mastocytosis had been antihistamines. Even with the advent of both H_1 and H_2 receptor blockers, only partial relief of symptoms has been obtained with these drugs. Because of the presence of increased amounts of prostaglandin D_2 metabolites in the urine of patients with mastocytosis, aspirin therapy has been used for this disorder[141] and may partially ameliorate symptoms, particularly hypotension, while decreasing the amounts of urine prostaglandin D_2 metabolites. Oral adminis-

TABLE 6.—*A Comparison of Mastocytosis and Carcinoid Syndrome*

Clinical Findings	*Description*	
	Mastocytosis	*Carcinoid*
Urine content	Histamine	Serotonin
Skin lesions	Urticate	Pellagra-like
Flush appearance	Red	Cyanotic
Duration of flush	30 Minutes	10 Minutes
Pruritus	Present	Rare

tration of sodium cromoglycate, a drug felt to stabilize mast cell membranes and thereby inhibit mediator release, has been shown to significantly decrease subjective symptoms.[145] In one case report, a single dose of mithramycin alleviated pain caused by mast cell infiltration of bone.[146]

Conclusion

Mast cells are uniquely positioned at sites of host-environment interactions, armed with receptors for IgE and other secretagogues and loaded with a supply of potent biologically active mediators. They thus may play a role in homeostatic regulation of the host-environment interface. In addition, these properties of mast cells enable them to participate in processes perceived as disease rather than homeostasis. Such disorders include the family of allergic diseases (asthma, rhinitis, urticaria) and nonallergic problems as well. In fact, the recruitment of mast cells in non-IgE-mediated processes may well be an important and often overlooked pathophysiologic sign of diseases as varied as cystic fibrosis, ulcerative colitis and neoplasia. Only as histopathologic assessment of disease focuses on mast cells and the biochemical identification of mast cell mediators is refined can the understanding of the role of this cell proceed from speculation to knowledge.

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