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THE URTICARIAL DISORDERS: FROM PRURITUS TO VASCULITIS

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INTRODUCTION

Urticaria and angioedema are commonly encountered clinical entities that represent primary skin reaction patterns to a number of different stimuli including some systemic diseases. Frequently these skin lesions occur in the same patient. In a report by Warin and Champion (1974), 49% of their patients had both urticaria and acquired angioedema, 40% had urticaria alone, while 11% only had angioedema. Although urticaria and angioedema may arise in all age groups, acute disease (lasting less than 6 weeks) appears to be more common in young adults and children, and frequently results from the triggering of cutaneous mast cells through antigen-specific IgE antibodies. The chronic form of urticaria/angioedema is generally accepted as lasting longer than 6 weeks, and occurs much more frequently in adults, especially middle-aged females. Although the cutaneous mast cell is centrally involved in the chronic form of this disorder, it appears that a role for IgE antibodies is less certain (Green et al., 1965; Monroe and Jones, 1977; Mathews, 1983). The cumulative prevalence of urticaria/angioedema in the general population has been reported to range from approximately 15% to 20% (Swinny, 1941; Matthews, 1983). Available data on the natural disease history of these disorders among large groups of patients indicate that 50% of individuals with urticaria alone are free of lesions after one year, while 20% continue to experience their eruption for more than 20 years. Similarly, approximately one-half of patients with acquired angioedema alone continue to have their disorder for more than one year. In patients with both urticaria and angioedema, 75% experience symptoms for more than one year, half for greater than five years, and 20% for more than twenty years (Warin and Champion, 1974). A personal or family history of an atopy may be more common in patients with acute urticaria; but this association does not appear to be a factor in patients with chronic urticaria/angioedema (Swinney, 1941; Champion et al., 1969).

CLINICAL MORPHOLOGY OF URTICARIA AND ANGIOEDEMA

Because they are so common, the lesions of urticaria are often correctly diagnosed by the patient. Classically, this cutaneous eruption appears as well-defined, round to oval, white or erythematous papules. Surrounding erythema. may or may not be present. These lesions range in size from a few millimeters to several centimeters in diameter. Less commonly, central clearing or coalescence of expanding urticarial papules leads to annular, arcuate, or serpiginous configurations. The primary site of pathology in urticarial lesions is localized to the dermis and this is evident clinically by: 1) insignificant alterations in epidermal surface markings (no scaling), 2) normal melanocytic pigmentation, and 3) the presence of erythema representing dermal vessel dilatation. Lesions are usually pruritic and generally last less than 24 hours. The eruption of "giant hives" or angioedema arises deep in the dermis or in the subcutaneous tissue, and appears as large, slightly erythematous areas with a normal epidermal surface and poorly-defined borders. Often these subcutaneous swellings are asymptomatic, but may be slightly painful. Typically the lesions are asymmetrical and may involve any anatomical area; however, prevalent sites of involvement include: the periorbital and perioral areas, the tongue, hands, feet, scrotum, and less commonly the larynx and gastrointestinal tract.

HISTOPATHOLOGIC CHANGES OF URTICARIA AND ANGIOEDEMA

Classically, cutaneous biopsies of typical urticarial lesions have been reported to have surprisingly few histopathologic alterations. Minimal to moderate perivascular cellular infiltration, consisting primarily of mononuclear cells, and in some cases eosinophils, is often described. Dilatation and engorgement of superficial vessels and lymphatics in association with dermal edema is another prominent feature. A recent study of twenty-four patients with chronic urticaria, however, indicates that a greater spectrum in histopathologic changes may be observed. Lesional skin biopsies from eleven of these patients showed the pathologic changes frequently described for urticaria. On the other hand, ten subjects had evidence of a dense perivascular infiltrate consisting of mononuclear cells, neutrophils and eosinophils. No leukocytoclasis or endothelial cell damage, however, was evident. In the three remaining patients, a true vasculitis was observed in lesional skin specimens. These changes were characterized by a neutrophil-rich perivascular infiltrate associated with leukocytoclasis and fibrinoid material deposition in dermal vessel walls. Direct immunofluorescence studies demonstrated IgM antibody, C_3 and/or fibrin in all three patients suggesting the presence of immune complex disease (Jones et al., 1983). In another study, Natbony and coworkers (1983) reviewed duplicate skin biopsies from 43 patients with idiopathic chronic urticaria. Evidence of a leukocytoclastic vasculitis was observed in only one patient. In the remaining patients, a four-fold increase in mononuclear cells was seen. In eight of the forty-three patients a ten-fold elevation in resident dermal mast cells was observed in lesional skin compared to cutaneous biopsies from normal controls. Mast cell degranulation frequently was evident in these lesional specimens. Although an increase in dermal mast cells is an intriguing explanation for the pathogenesis of urticaria, a recent study from our laboratory using a morphometric method of point counting has not confirmed that lesional tissue mast cells are increased in chronic urticaria patients (Kasper et al., 1986). The histopathologic changes in angioedema have been less well investigated; however these lesions demonstrate vasodilatation and edema formation and a mixed cellular infiltrate. In contrast to the more superficial pathology of urticaria, these alterations are observed primarily in the deep dermis and subcutaneous tissue.

Investigation of the pathophysiologic events responsible for urticaria/angioedema reactions strongly implicate the cutaneous mast cell and the release of its mediators as the initial effector "system" for these skin eruptions. Because of the increasing recognition of the diverse consequences of mast cell degranulation, it has been possible to identify a number of mediators generated and released by this cell. Likewise, as our understanding of the forces responsible for mast cell secretion have advanced, it is now appreciated that different stimuli, both immunologic and non-immunologic, may be responsible for the clinical expression of urticaria and angioedema. In order to better understand the underlying mechanisms responsible for urticarial and angioedema reactions, a brief review of the mast cell, its mediators, and its response to different stimuli is presented in the following section.

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). 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 (Figure 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 when examined by light microscopy. 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 (Figure 1B). These apparent structural differences between rodent and human mast cells are not understood.

Histologic 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

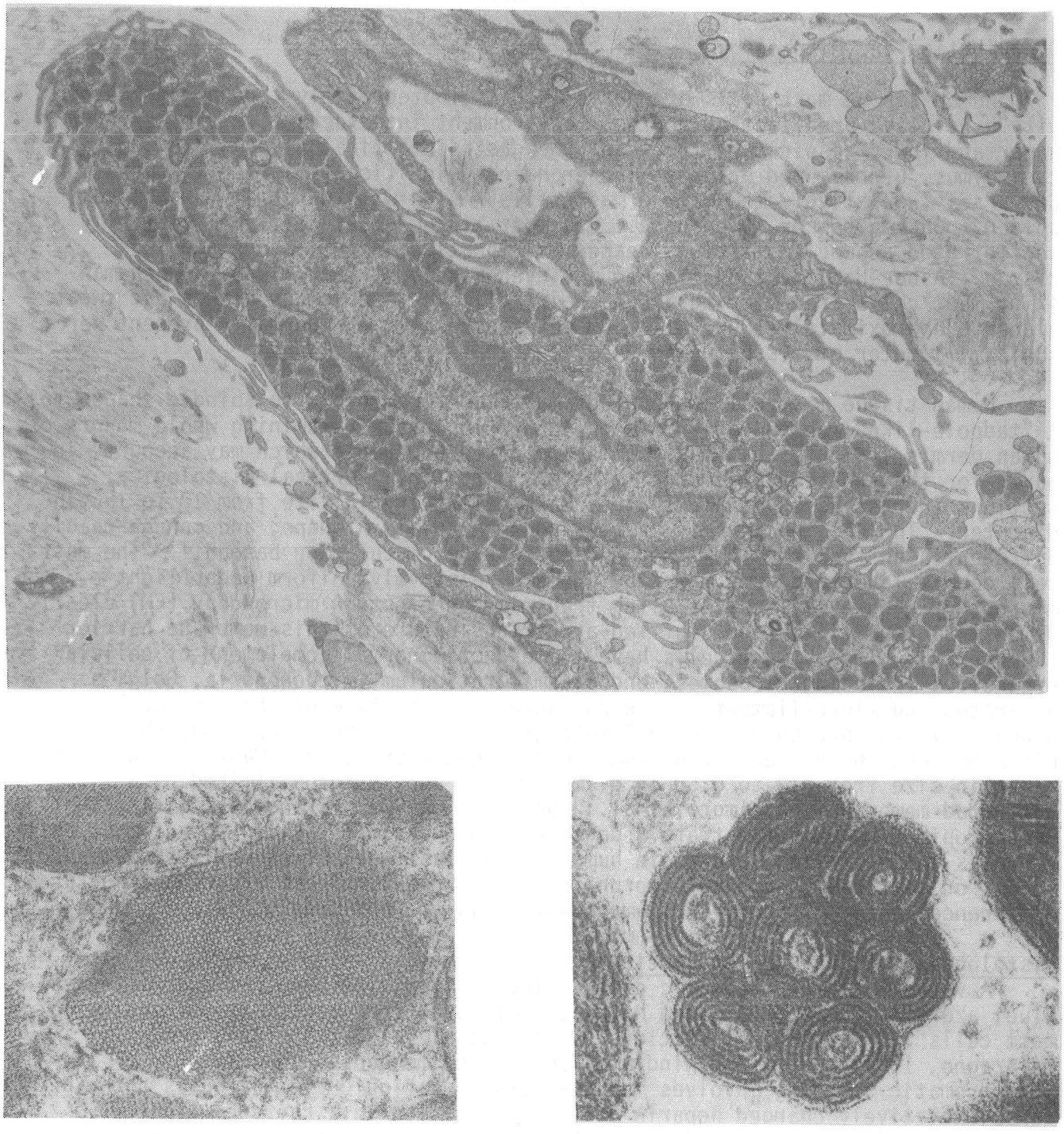


Fig. 1. Transmission EM of a human cutaneous mast cell. Varying morphology of internal structures within mast cell granules are shown.

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. 1985). 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 quantifying mast cells in tissues (Kasper et al., 1986).

Mast Cell Origin

Since its identification over 100 years ago, a number of putative mast cell precursors have been suggested including: primitive mesenchymal cells, fibroblasts, lymphocytes and thymocytes. (Fawcett, 1955; Johnstone, 1956; Csaba, 1960). In rodents, 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; Udoji and Razavi, 1975; 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 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 I and III). 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 granule matrix and its associated mediators may remain in tissues for hours until complete dissolution occurs or they become phagocytosed. The newly-formed mediators (prostaglandins and leukotrienes), which are generated from arachidonic acid at the time of mast cell stimulation, are released from the cell within several minutes after exposure to a secretory agonist. Taken together, these observations indicate that following mast cell activation, a series of inflammatory events may occur that are dependent in part on the temporal release of preformed and newly-generated mediators.

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). The histamine content of human mast cells ranges from 4 to 5 pg/cell (Schulman et al., 1982; Tharp et al., 1985), and under normal conditions, histamine concentrations in the circulation range from 0.2 to 0.4 ng/ml. 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 also is 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 a 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) (Figure 2).

The intradermal injection of histamine results in the "triple response of Lewis" which initially appears as a localized pruritic area of erythema that evolves into an edematous wheal surrounded by an extending area of redness (flare) (Lewis, 1927). The ability of histamine to provoke an urticarial response in the skin and the presence of elevated histamine levels in various biologic fluids in patients with urticaria have suggested a central role for this mast cell mediator in the pathogenesis of an urticarial response. Significantly elevated histamine levels in both skin blister fluids and cutaneous biopsy specimens of lesional tissue from patients with various forms of urticaria have supported this notion (Kaplan, et al., 1978; Phanuphak, et al., 1980).

The biologic effects of histamine release are mediated by two receptor subtypes, conventionally termed histamine$_1$ (H_1) and histamine$_2$ (H_2) receptors. H_1 and H_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 I). 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, 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 cyclic AMP levels in human leukocytes and pulmonary cells, while

activation of the H_1 receptor results in increased cyclic GMP concentrations (Bourne et al., 1973; Platshon and Kaliner, 1978). Several reports have indicated that both H_1 and H_2 receptors may be important in the expression of cutaneous vasodilatation; however, the use of H_2 antagonists alone have not been shown to significantly alter histamine-induced skin reactions (Summers et al., 1981; Commens and Greaves, 1978). Thus, it appears that histamine's predominant effect on the cutaneous vasculature is through the H_1 receptor.

Because of its wide range of physiologic 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 1.6 to 2.5 ng/ml (Kaliner et al., 1982). Inhibition of these systemic symptoms by pretreatment with anti-histamines can be achieved by the use of both H_1 and H_2 receptor antagonists is necessary (Table II). These observations underscore the clinical relevance of systemically released histamine in mast cell-mediated events, and in contrast to the skin emphasize the necessity of combined H_1 and H_2 antihistamines for effective therapy for controlling non-cutaneous responses.

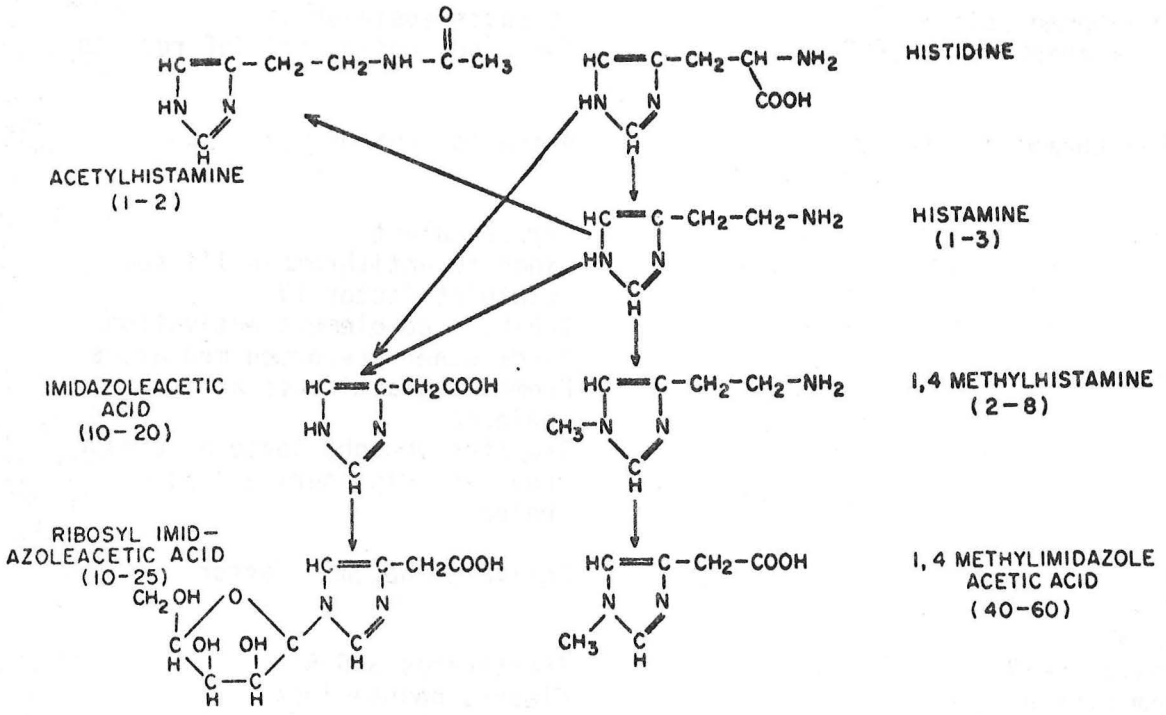


Fig. 2. Histamine metabolism. Histamine is formed (45, 46) by decarboxylation or histidine (histidine decarboxylase enzyme) and metabolized to specific metabolites—methylhistamine, methylimidazole acetic acid, and acetylhistamine. Imidazole acetic acid and its ribose conjugate are nonspecific metabolites. Numbers in parentheses refer to per cent of exogenous histamine excreted

Table I

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 bradykinin		Activates Hageman Factor
* 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.

Table II 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: Because some patients with urticaria and angioedema are unresponsive to H_1 blockers or a combination of H_1 and H_2 antagonists it has been suggested that other mediators (and possibly cells other than mast cells) may be important in the expression of these cutaneous eruptions. This hypothesis is further supported by the observation that a variable number of inflammatory cells are observed in histologic sections of urticarial lesions (Natbony et al., 1983). Several different 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 I). 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). Interestingly, the deposition of eosinophil-derived major basic protein (MBP) has been demonstrated in the dermis of lesional skin of patients with chronic urticaria. Peters and coworkers (1983) reported that 12 of 28 patients with chronic urticaria had MBP localized to blood vessels or more diffusely dispersed among connective tissue fibers in lesional skin biopsies. Because MBP can also provoke mast cell mediator release, both the local and systemic release of this protein from eosinophils may be important in some urticarial/angioedema reactions.

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). Despite these important physiologic influences, detectable abnormalities in coagulation and complement generation are not observed in patients with urticaria and angioedema.

LYSOSOMAL ENZYMES: The human and rodent mast cell has a number of granule-associated enzymes including tryptase, chymotryptase, arylsulfatase, β-hexosaminidase, β-glucuronidase, β-galactosidase, superoxide dismustase, and peroxidase (Table I). 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 which in turn could lead to bradykinin formation (Figure 3). The generation of kinins has been associated with pain, increased vascular permeability and smooth muscle contraction and thus may play a role in some acquired forms of urticaria/angioedema. In addition, the 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 potentially toxic molecules. The overall in vivo relevance of these granule-associated enzymes following mast cell secretion remains to be demonstrated.

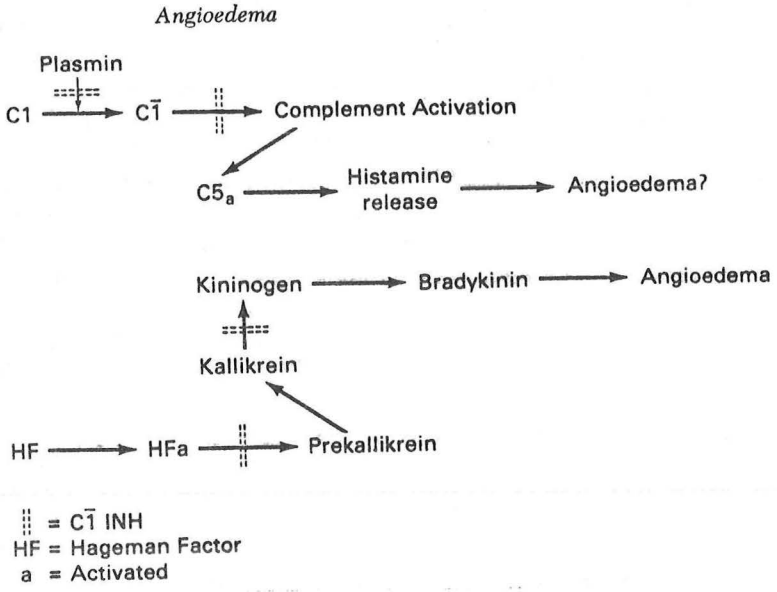


Fig. 3. Activation of complement pathway and plasma kinin-forming system of intrinsic coagulation pathway that may result in the development of angioedema. Note the different sites of action of C11NH in each pathway.

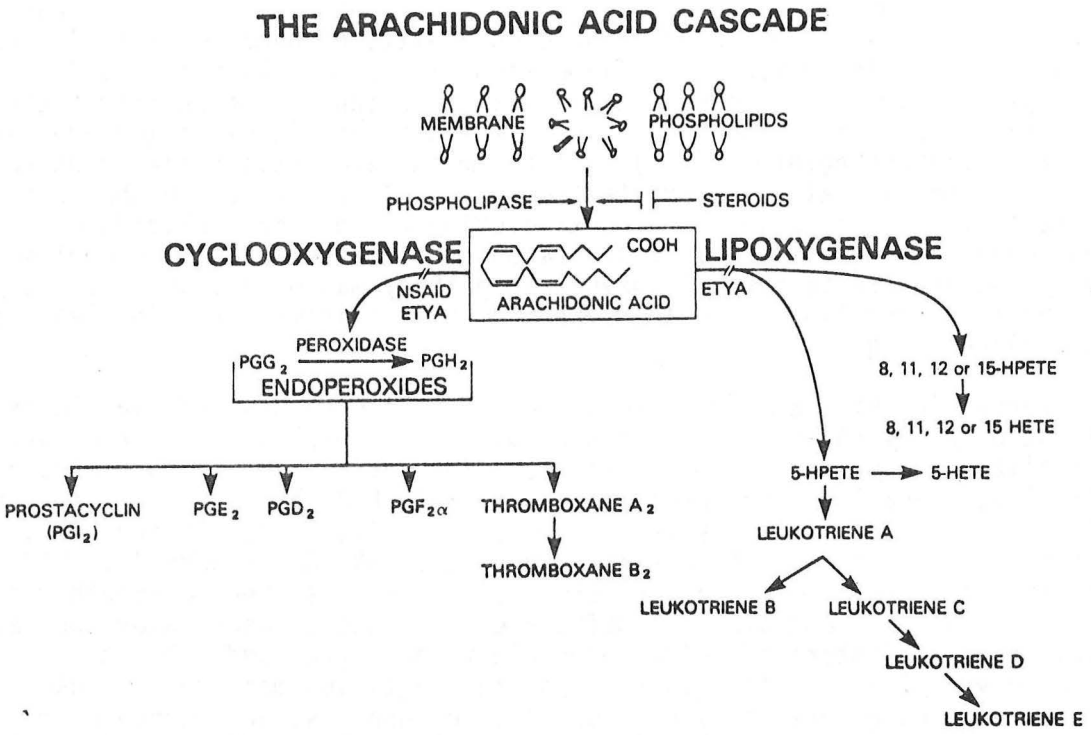


Figure 4. Arachidonic acid metabolism. Leukotriene formation via the lipoxygenase pathway. Prostaglandin D_2 (PGD_2) generation per the cyclo oxygenase pathway.

Newly-Formed Mediators:

The role for mast cell-derived vasoactive mediators in the pathogenesis of urticaria has been supported by a series of histologic, biochemical and pharmacologic studies. In addition to the preformed mediator histamine, at the time of stimulation the mast cell also generates oxidative metabolites of arachidonic acid via both the cyclooxygenase and 5-lipoxygenase pathways which have significant vasodilating effects. 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 4). PGD_2 mimics many of the local and systemic effects of histamine (Table III); 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 from two to six hours, and is capable of potentiating the vasopermeable effects of histamine and arachidonic acid-derived leukotrienes (Flower et al, 1976; Soter et al., 1983). In addition, PGD_2 is chemotactic for neutrophils, and when administered

intradermally induces a biphasic perivascular neutrophil infiltrate detectable at 30 minutes and 6 hours after injection (Soter et al., 1983). As PGD_2 appears to be the predominant arachidonic acid metabolite of human mast cells and capable of inducing cutaneous inflammation, it seems likely that this molecule would play an important role in urticarial reactions. Interestingly however, treatment of patients with cyclooxygenase inhibitors (aspirin and nonsteroidal anti-inflammatory agents, NSAIA) fail to ameloriate urticaria/angioedema, and in some instances actually exacerbate the pathologic process. In the latter case, the mechanism for this apparent contradiction has not been elucidated. It has been suggested, however, that a diversion of arachidonic acid metabolism from the cyclooxygenase to the 5-lipoxygenase pathway may occur, and thus actually augment the production of another group of pro-inflammatory molecules, the leukotrienes (Figure 4).

Conversion of arachidonic acid via the 5-lipoxygenase pathway leads to the production of hydroperoxy-eicosatetraenoic acids (HPETEs) which are further metabolized to hydroxy-eicosatetraenoic acids (HETEs) and leukotrienes (LTs). Initially, 5-HPETE is converted to the unstable LTA which in turn gives rise to 5,12-di-HETE (LTB) or the cysteinyl-containing LTs, (LTC, LTD and LTE), formerly termed slow reacting substances of anaphylaxis (SRS-A) (Figure 4). LTC, LTD and LTE promote microvasculature vasopermeability and also induce smooth muscle constriction. LTB and other di-HETEs are less potent vasodilators but are significant activators of polymorphonuclear leukocytes and inhibitors of T-lymphocytes (Table III). In addition to the tissue mast cell, leukotrienes are known to be generated by neutrophils, eosinophils, and monocytes-macrophages (Borgeat and Samuelsson, 1979; Thompson et al., 1982; Weller et al., 1983). The intradermal administration of LTC, LTD, and LTE in man results in an immediate erythematous wheal and flare response in association with central pallor. Wheal formation peaks at 1 hour and resolves over the next 3 hours, while the erythematous response reaction more slowly (6 hours) (Soter et al., 1983). Cutaneous biopsies of LTC and LTD injection sites at two hours demonstrate dilatation of both superficial and deep vessels without cellular infiltration. In contrast to the pruritus induced by histamine, LTC and LTD more often provoke a burning or stinging sensation upon injection. LTB also elicits a transient wheal and flare reaction; however, its major clinical effect is a delayed erythematous cutaneous reaction characterized histologically by edema and neutrophil infiltration. The following observations implicate a role for LTs in the expression of urticaria/angioedema: (1) Vascular dilation and permeability induced by LTs persist longer than other vasoactive mediators (i.e., histamine and bradykinin) thus potentially explaining the persistence of urticarial lesions for several hours; (2) the vasoactive effect of LTs are not altered by histamine antagonists, and hence may provide one explanation for the resistance of some patients with urticaria to antihistamine therapy, and (3) LT generation is inhibited by corticosteroids through the production of a selective phospholipase inhibitor, lipomodulin. This observation could explain in part the beneficial effect of corticosteroid therapy in most urticarial syndromes.

Table III
NEWLY-FORMED HUMAN MAST CELL MEDIATORS

Mediator	Arachidonic Acid Metabolic Pathway	Effect
HHT	Cyclooxygenase	Chemotactic for Neutrophils and Eosinophils
Prostaglandin D_2*	Cyclooxygenase	Contracts smooth muscle Increases vascular permeability Increases cAMP Chemotactic for Neutrophils
HETE, LTB	Lipoxygenase	Chemotactic for Neutrophils and Eosinophils
Leukotriene C* Leukotriene D* Leukotriene E	Lipoxygenase	Constricts smooth muscle Increases vasopermeability Vasodepressors Synergistic with histamine Promotes prostaglandin generation

* Demonstrated in human mast cells.

Mast Cell Secretagogues

Degranulation of tissue mast cells results from both immune and non immune-mediated mechanisms (Table IV). 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 wheal and flare 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 ($\sim$1000ng/ml), circulating basophils, and presumably tissue mast cells, have up to 95% of their receptors occupied by this immunoglobulin (Malveaux et al., 1978). Antigen-specific IgE antibodies appear to play an important role in the pathogenesis of some acute urticarial reactions. 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* (Tharp and Sullivan, 1985). The anaphylatoxins have a rank order of potency in which $C_{5a} > C_{3a} > C_{4a}$ with C_{5a} being approximately 100-fold more potent than C_{3a}. (Hartman and Glovsky, 1981). Immune complex formation and subsequent anaphylatoxin generation may be an

important mechanism for mast cell activation in patients with urticarial vasculitis. In addition, eosinophil granule-derived MPB has been demonstrated to provoke mast cell degranulation in vitro (O'Donnell et al., 1983). The clinical significance of this observation is underscored by the recent report of MBP deposition in lesional skin of some patients with chronic urticaria (Peters et al., 1983).

A number of other naturally occurring and exogenous nonimmune agents also appear capable of stimulating mast cell mediator release (Table IV). The adenine nucleotides, ATP and ADP, and the neuropeptides, substance P, and calcitonin gene-related peptide (CGRP) have been demonstrated to be potent human mast cell secretagogues both in vitro and in vivo (Tharp et al., 1981; Coutts et al., 1981; Erjavec et al., 1981; Jorizzo et al., 1983; Piotrowski and Foreman, 1986). These molecules have potential clinical relevance since there are several known neural sources of extracellular ATP, ADP, substance P, and CGRP in close proximity to tissue mast cells. 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). A number of pharmacologic agents including narcotics, d-tubocurarine, succinylcholine, aspirin, NSAIA, polymyxin B, vancomycin and thiamine have been implicated in direct (non IgE-mediated) mast cell activation.

Table IV

CLINICALLY RELEVANT HUMAN
MAST CELL SECRETAGOGUES

Immunologic mechanisms

- IgE-mediated
- Anaphylatoxins (C_{3a}, C_{4a} & C_{5a})
- Lymphokines
- Eosinophil major basic protein (MBP)

Non Immunologic mechanisms

- Medications (Narcotics, Curare, Succinylcholine, Aspirin, Nonsteroidal anti-inflammatory agents, Polymyxin B, thiamine, vancoymcin)
- Adenine Nucleotides (ATP, ADP)
- Peptides (Gastrin, ACTH, Estrogens, Substance P, CGRP)
- Radiocontrast media
- Complex carbohydrates
- Venoms
- Irradiation
- Heat

Clinical Responses to Mast Cell Mediator Release

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 these 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 focal, mast cell-mediated symptoms, 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 may induce symptoms localized to the gastrointestinal tract (Table V). In the skin, the primary clinical manifestations of dermal mast cell mediator release include pruritus and urticaria/angioedema. These symptoms and signs are believed to be mediated in great part by histamine, although arachidonic acid-derived LTs also may play a role. More generalized cutaneous flushing (head, neck and upper chest) is a clinical manifestation associated with increased circulating levels of histamine and/or PGD_2 (Kaliner et al., 1982; Roberts et al., 1980).

Table V

CLINICAL MANIFESTATIONS OF
MAST CELL SECRETION

Anatomical Region	Clinical Manifestations
Skin	Pruritus, urticaria, angioedema, pain, flushing, late phase reaction
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
Central Nervous System	Headache, dizziness, syncope

Late Phase Reactions (LPR)

It has now become clear that both immunologic and non-immunologic mast cell degranulation in vivo may result in a typical immediate wheal and flare response followed several hours later by burning, pruritus, erythema and induration at the site of injection. This "late phase reaction" (LPR) generally peaks at 6 to 8 hours and resolves by 24 hours. Skin testing for immediate hypersensitivity reactions in allergic individuals may result in isolated immediate responses (wheal and flare), immediate and delayed reactions, or isolated LPRs with a respective incidence of 20%, 66%-85% and 6%-14% (Miller, 1961; Richerson et al., 1979). Histopathologic alterations of LPR at the time of maximal reactivity are characterized by a mixed perivascular cellular infiltrate consisting of mononuclear cells, neutrophils, eosinophils, and some basophils. Vasodilatation without endothelial cell damage and edema formation are also prominent histopathologic features (Solley et al, 1976; Richerson et al., 1979). At 24 hours, the cellular infiltrate is sparse and predominantly mononuclear. Studies performed in both rodents and humans indicate that LPRs result directly from mast cell degranulation. A low molecular weight factor of 1400 daltons consisting of twelve amino acids has been isolated from rat mast cell granules which is capable of producing an LPR when injected intradermally. This factor has been termed inflammatory factor of anaphylaxis (IF-A) (Oertel and Kaliner, 1981). To date the presence of IF-A or similar molecules has not been demonstrated in human mast cells. However, because human mast cells are known to release a number of mediators capable of simulating IF-A-like activity (Tables I and III), the following pathogenesis for LPR can be postulated. Following stimulation by a variety of potential mechanisms (Table IV), mast cell degranulation leads to the release of both preformed and newly-generated mediators including histamine, chemotactic factors and arachidonic acid metabolites. Vasodilatation, increased vascular permeability and inflammatory cell infiltration results (Figure 5). The neutrophils that accompany this inflammatory cell response appear to be necessary for the subsequent mononuclear cell predominance in a LPR. Pharmacologic studies have demonstrated that combined H_1 and H_2 antihistamines or corticosteroids can suppress a LPR, while aspirin pretreatment is without an effect. These observations indicate a significant role for histamine and leukotrienes, but not prostaglandins, in this reactive process (Smith et al., 1980; Slott et al., 1975). Clinically, delayed urticarial responses to physical stimuli such as pressure or vibration closely resemble LPRs. The clinical similarities between LPRs and delayed pressure urticaria are summarized in Table VI.

CONSEQUENCES OF MEDIATOR RELEASE

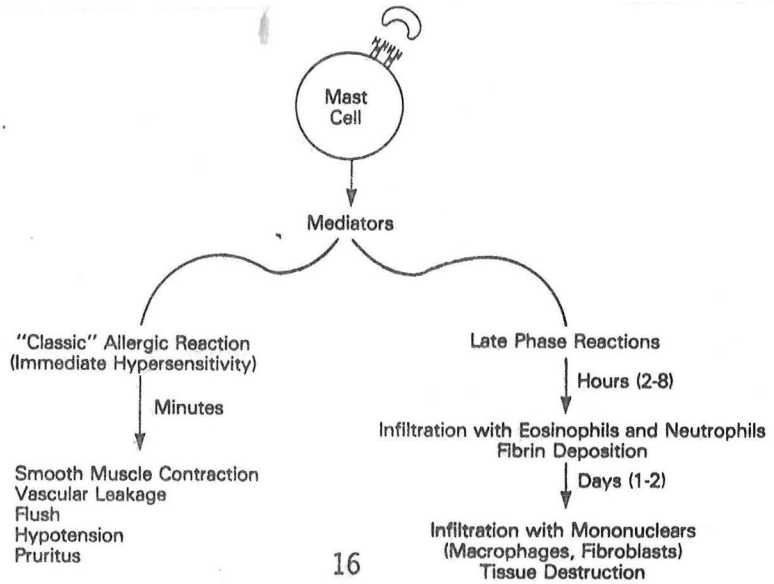


Fig. 5

Table VI. Similarities between delayed urticarial reactions and late-phase reactions

	DELAYED URTICARIAL REACTIONS TO PHYSICAL STIMULI	HUMAN CUTANEOUS LATE-PHASE REACTIONS
Clinical appearance	Erythema and induration +/− immediate wheal and flare	Erythema and induration Follows immediate wheal and flare
Time Course	Peak 6 to 12 hours Resolves 24 to 48 hours	Peaks 6 to 8 hours Resolves 24 hours
Microscopic appearance		
Cellular	Primarily mononuclear or Mixed cell infiltrate	Mixed cell infiltrate
Humoral	No deposition of immunoreactants*,†	No deposition of immunoglobulins or complement (+/− fibrin)
Pathogenesis	Mast cell products released*,†	Mast cell products released

*Delayed pressure urticaria/angioedema
†Delayed vibratory urticaria/angioedema

PATHOGENESIS OF URTICARIA/ANGIOEDEMA

A primary role for the tissue mast cell in the expression of urticaria/angioedema is supported by numerous clinical and pharmacologic studies. The early vascular changes observed in these cutaneous eruptions can be readily attributed to the release of the preformed mediator, histamine, but also may include the elaboration of mast cell-derived PGD_2 and LTs. Following stimulation, the tissue mast cell also may release several different chemotactic factors (histamine, NCF, ECF-A, and possibly LTB) that result in the influx of inflammatory cells to the primary site of mast cell activation. It is likely that the infiltration of activated leukocytes into the area leads to the release of additional inflammatory cell-derived mediators resulting in local tissue injury and possibly provoking a second wave of tissue mast cell activation (Figure 6).

Although this series of events theoretically could explain in total the pathogenesis of urticaria/angioedema, evidence suggests that the local release of neuropeptides from sensory nerve endings also may play a role in the expression of these cutaneous eruptions. In his original observation, Lewis (1927) demonstrated that the triple response to injury in the skin was mimicked by the intradermal injection of histamine and that the flare component of this cutaneous reaction was dependent on an intact neural network within the skin. This latter observation led Lewis to postulate that the vasodilatation seen in normal subjects resulted from antidromic stimulation of cutaneous sensory nerve endings. Subsequent studies have supported this hypothesis. Inflammatory

responses in the skin induced by topical chemical irritants are blocked by severing the dorsal nerve root distal to, but not proximal to, the dorsal root ganglion (Bruce, 1913). Furthermore, it is known in man that damage to the brachial plexus leads to a marked reduction in flare and, to a lesser extent, wheal responses in the skin when the plexus is damaged distal to the dorsal root ganglion (Bonney, 1954). Thus, these observations support the contention for a neurologically-mediated component (axon reflex) in the triple response of Lewis. Subsequent studies have suggested that the release of the neuropeptide, substance P (SP), from sensory nerve endings following antidromic stimulation may represent this neurogenic mechanism. Substance P is a peptide with eleven aminio acid residues that is present in both the central nervous system and in peripheral nerves, including C-type sensory nerves found in the skin. The intradermal injection of this neuropeptide in man results in a dose-related wheal and flare response. Stimulation of sensory nerves provokes the release of SP which results in vasodilation and plasma extravasation. Depletion of SP in these nerve endings with the reagent, capsaicin, results in blockade of antidromically-induced vasodilatation. Recent studies indicate that the wheal and flare response associated with SP release may be mediated by two separate mechanisms. Several reports have convincingly demonstrated that the flare reaction induced by SP is predominantly the result of mast cell histamine. Indeed, SP has been demonstrated in vitro to stimulate histamine release from rat mast cells. SP-induced edema (wheal) formation, however, appears to result from a direct effect of this peptide on dermal venules (Piotrowski et al., 1983). The model proposed for the interaction of sensory nerves with tissue mast cells is illustrated in Figure 6, and suggests that cutaneous sensory nerves are activated through some stimulus or by mast cell histamine release. Action potentials are generated orthodromically and ultimately reach the spinal cord via the dorsal horn. This stimulus is subsequently relayed to sensory centers in the brain. Simultaneous with this orthrodromic conduction, antidromic (retrograde) impulses also are generated under certain conditions and spread through the terminal arborizations of the sensory nerve resulting in local SP release. Substance P in turn stimulates tissue mast cells to secrete preformed, and possibly newly-formed, mediators which lead to vasodilatation and conceivably further stimulation of other sensory endings. As mentioned previously, SP also appears to contribute to the wheal and flare response by its direct effect on dermal endothelial cells. Recently, a second neuropeptide, termed calcitonin gene-related peptide (CGRP) has been identified in the same sensory nerve endings that contain SP. CGRP contains 37 amino acid residues and has a wide distribution in both neuronal and glandular tissues. Like SP, this molecule stimulates mast cell histamine release in vitro and provokes a dose-related wheal and flare reaction in vivo. A recent report indicates that the flare response, but not the edema formation induced by CGRP, is inhibited by antihistamine pretreatment. Interestingly, unlike SP, CGRP has been observed to produce a delayed erythematous, slightly painful lesion at the site of injection following an initial wheal and flare reaction. This local reaction peaked at 1 hour and persisted for more than 3 hours after injection. Histopathologic examination of these cutaneous sites have demonstrated significant infiltration by polymorphonuclear leukocytes. Pretreatment with antihistamines and indomethacin have failed to inhibit this delayed cutaneous response to CGRP. Because its primary effects are delayed, it has been postulated that CGRP either is chemotactic itself or induces the release of chemotactic molecules from other cells (possible mast cells). Furthermore, these observations suggest that

the polymorphonuclear cells accumulating at the site of stimulus most likely generate and release mediators (possibly LTs) that lead to vasodilatation (Piotrowski and Foreman, 1986).

Taken together, it can be postulated that following a local stimulus in the skin tissue mast cells release mediators which lead to vasodilatation, plasma extravasation, inflammatory cell chemotaxis and sensory nerve stimulation. The subsequent generation of antidromic sensory nerve potentials results in the local release of SP and CGRP. These neuropeptides in turn further promote vasodilatation and edema formation, by their direct effects on endothelial cells and through the stimulation of resident dermal mast cells. The release of chemotactants leads to the local infiltration of inflammatory cells. The number of infiltrating leukocytes and their degree of activation may dictate the severity, and hence, duration of the inflammatory reaction. Because leukocytes are known to stimulate mast cell mediator release, it is conceivable that these cells may perpetuate the initial reaction. Furthermore, the elaboration of leukocyte-derived lysosomal enzymes and other inflammatory mediators in the local environment may also lead to additional sensory nerve stimulation and subsequent SP and CGRP release. Clinically, there is some evidence that an ongoing inflammatory "cycle" may be present in some patients with urticaria and possibly account for the chronicity of their disorder. This is supported by several observations. Cohen and Rosenstreich reported that the normal appearing skin of patients with urticaria was 100-fold more sensitive to the intradermal mast cell degranulating effects of codeine when compared to the cutaneous reaction of other allergic individuals and normal controls (Figure 7). In addition, several studies have shown that tissue and fluid histamine concentrations are elevated not only in lesional but also normal skin sites in some urticarial patients (Kaplan et al., 1978). Furthermore, late phase reactions have been reported to occur in nonlesional skin of patients with urticaria following the intradermal injection of histamine (Juhlen and Michaelsson, 1969). These studies are supported clinically by the fact that many patients with urticaria also are dermographic. Taken together, these observations suggest the presence of ongoing "subclinical" inflammatory activity in the normal appearing skin of patients with urticaria. From our understanding to date, it appears that the clinical expression of urticaria/angioedema results from a combination of pathophysiologic events that include mast cell activation and the elaboration of mediators, the local release of sensory nerve peptides and the infiltration of inflammatory cells.

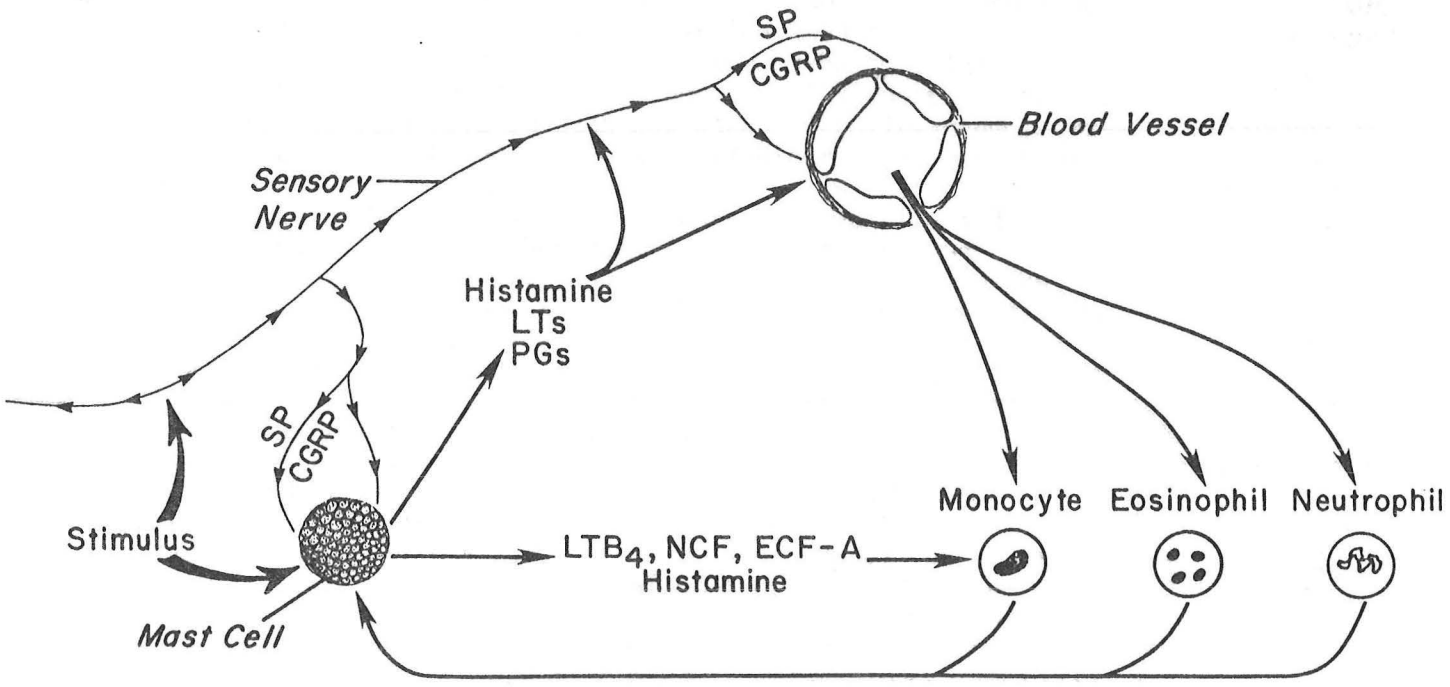


Figure 6. Pathogenesis of urticaria/angioedema

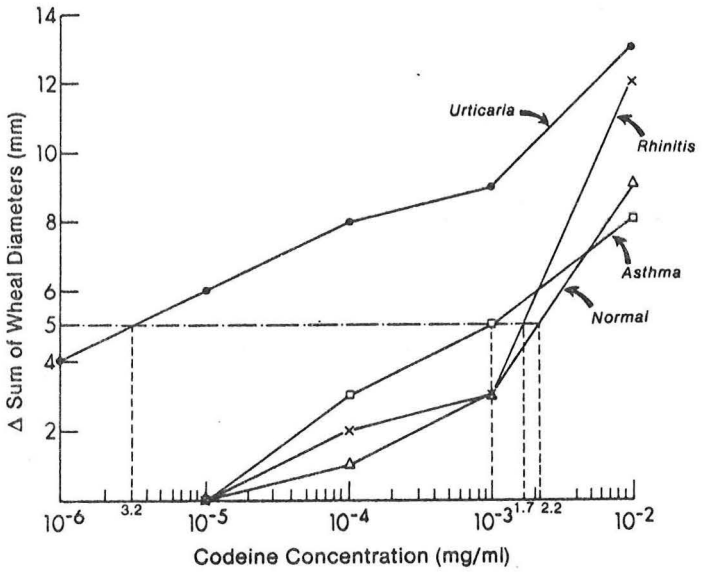


FIG. 7. Codeine skin testing in urticaria-prone subjects, subjects with asthma and rhinitis, and normal subjects. The Δ sum of the wheal diameters induced by each concentration of codeine was determined in four individuals. The CD_5 was determined by extrapolation to the X axis as indicated by the *dashed vertical lines.* Results represent the arithmetic means of the four individual responses at each concentration.

URTICARIA: POTENTIAL CAUSES

The clinical expression of urticarial lesions in an individual patient represents a cutaneous reaction pattern for which there may be multiple, etiologies. Historically, it has been stated that children more commonly experience episodes of acute urticaria (≤ 6 weeks duration) in which the underlying mechanism is often related to antigen-specific coupling of mast cell surface bound IgE antibodies. Chronic urticaria, however, appears to occur more often in adults and result from IgE-independent mechanisms (Green et al., 1965; Monroe and Jones, 1977 and Mathews, 1983). For an individual patient, these generalities offer little help in considering potential etiologies for an urticarial reaction. Numerous agents have been implicated in provoking urticarial eruptions and include: medications, foreign sera, foods, food additives, infections, insect bites and stings, contactants, inhalants, and physical forces (heat, light, cold, pressure). In addition, urticarial reaction patterns have been associated with some genetic disorders, pregnancy, connective tissue diseases and neoplasms (Table VII). While the origin of acute urticaria often can be detected, an etiologic agent or precipitating cause is established in only 20 to 25 percent of patients with chronic urticaria. However, because of the significant morbidity (pruritus and cosmetic problems) and potential for uncovering an associated systemic disorder, a thorough evaluation of a patient with a chronic urticarial reactions is warranted.

Table VII

Potential Causes of Urticarial Reactions

- Medications
- Foreign Sera
- Food
- Food additives
- Infections
- Insect bites and stings
- Contactants
- Inhalants

- Physical Agents (Heat, cold, pressure and light)

- Diseases
  - Genetic disorders
  - Connective Tissue Diseases
  - Neoplasms

- Pregnancy

Medications

Penicillin remains one of the most common causes of medication-induced urticaria, and is mediated through the coupling of specific mast cell-bound IgE antibodies. Allergy to penicillin or its metabolites can be readily detected by conventional prick or intradermal skin testing. It is important to remember that traces of penicillin may be found in various dairy products, and thus could potentially provoke an urticarial reaction in a penicillin-sensitive patient. A number of different medications also have been identified which have the ability to stimulate mast cell mediator release independent of IgE antibodies. These agents include: morphine, codeine, vancomycin, polymxin B, curare, d-tubocurarine, thiamine, aspirin and NSAIA. The intradermal administration of morphine is a commonly practiced method for assessing human cutaneous mast cell reactivity *in vivo*, and has been demonstrated to mediate its action on mast cells through a naloxone inhibitable receptor (Casale et al., 1984). The intravenous administration of vancomycin has been associated with episodes of cutaneous flushing and urticaria. It appears that vancomycin can directly trigger mast cell mediator release independent of IgE antibodies. Because this vancomycin-induced reaction is concentration (rate of infusion) dependent, it can be prevented by decreasing the rate of drug administration. Urticaria/angioedema and anaphylactic responses to aspirin and NSAIA occur in approximately 1% of an outpatient population (Chafee and Settipane, 1974). Intolerance to these medications has been reported to range from 2 to 10 percent of patients with asthma and 20 to 50 percent of patients with existing chronic urticaria. Urticaria/angioedema may accompany asthma in sensitive individuals or may occur independently. In the latter case, the onset of urticarial lesions may be delayed for up to 20 hours after ingestion (Bruce-Pearson, 1963;

Moore-Robinson and Warin RP, 1967). Although the mechanism for aspirin induced/exacerbated urticaria is unknown, it has been hypothesized that inhibition of cyclooxygenase by salicylates results in the preferential metabolism of free arachidonic acid to leukotrienes via the 5-lipoxygenase pathway. The leukotrienes , LTC and LTD, are known to induce significant vasodilation when injected intradermally. A recent report has suggested that aspirin-sensitive patients may have an intrinsic defect in arachidonic metabolism. In the presence of aspirin, basophils from salicylate intolerant patients generated relatively greater proportions of LTD_4 than PGE_2 *in vitro* than did basophils from normal control subjects. These observations suggest that aspirin sensitive patients may be more prone to produce LTs in the presence of cyclooxygenase inhibition (Goetzl et al., 1986). It should be remembered that up to 15 to 20 percent of patients intolerant of aspirin also may react adversely to azo dyes, notably tartrazine, and benzoates (Michaelsson and Juhlin, 1973). Radiocontrast media also may provoke an urticarial response. As many as 5 to 8 percent of patients receiving intravenous radiocontrast media may have an adverse reaction (Whitten, 1975).

Foreign Sera

Urticaria is commonly observed in conjunction with the administration of blood, serum or immunoglobulins, and is felt to result primarily from the formation of immune complexes with subsequent complement activation and the formation of the mast cell stimulating anaphylatoxins ($C3_a$, $C4_a$ and $C5_a$). This mechanism has been clearly demonstrated in patients with antibodies to ^aIgA. Such antibodies occur in approximately 40% of patients with IgA deficiency, and in 15% to 20% of patients who have received multiple tranfusions (Wells et al., 1977; Vyas and Fudenberg, 1969). The administration of gamma globulin also has been linked to urticarial reactions in which IgG aggregates, capable of complement fixation, have been identified (Glaser and Wyss-Sonffront, 1961). Similarly, the use of heterologous serum resulting in immune complex disease and a serum sickness response frequently is accompanied by an urticarial eruption early in the disease process (Kohler, 1983).

Foods and Food Additives

Foods commonly have been implicated as a cause of acute urticaria, but appear to be less important in the chronic form of this disorder (Matthews, 1983). Fish, seafoods, nuts, peanuts and eggs are among the most common offenders, often through an IgE-mediated mechanism. The potential etiologic role of foods in immediate hypersensitivity reactions is underscored by a recent study in which skin testing to various foods was performed in 102 patients with idiopathic anaphylaxis. Patients included in the study had a history of at least two of the following symptoms: angioedema with/without urticaria, laryngeal edema leading to dyspnea, hypotension, or loss of consciousness. Of the 102 tested, 32 patients were skin-test positive to one or more foods. In seven of these patients, oral challenge of the specific food(s) provoked an anaphylactic reaction (Striker et al., 1986). In addition, food additives in the form of preservatives and dyes also may play a role in postprandial urticarial reactions. For example the antioxidants, sodium or potassium sulfites or metabisulfite commonly used on fresh vegetables, and added to wines, have been associated with acute urticaria accompanied by flushing, respiratory

distress and hypotension (Stevenson and Simon, 1981). Recently, recurrent episodes of urticaria/angioedema have been reported in 5 patients following ingestion of the low-calorie sweetener, aspartame (NutraSweet and Equal). In a preliminary double-blind study, aspartame-induced allergic reactions have been documented in five sensitive patients (Kulczycki and Danker, 1986). To date, the FDA has accumulated 61 reports of urticaria associated with aspartame consumption. The mechanism for this apparent mast cell-mediated reaction is presently unknown, but appears to be independent of IgE. Vegetable gums such as acacia, gum arabic, tragacanth, quince, carob seed and caregeenan also have been implicated as etiologic agents in urticarial reactions. As mentioned previously, salicylate, benzoate, and azo dye-containing foods also may trigger an urticarial response in aspirin-sensitive individuals; however, the frequency in which these agents are a primary cause of urticaria has been questioned. Urticaria patients who are skin test-positive to Candida organisms also have been reported to have cross-sensitivity to food yeasts. Some of these patients have benefitted from anti-candidal therapy and low yeast diets (James and Warin, 1971).

Infections

Various infectious agents have been implicated in provoking an urticarial reaction. Viral infections commonly have been identified as etiologic agents in acute urticarial reactions in children. In addition to mononucleosis and coxsackie virus infections, urticaria may precede the onset of jaundice in patients with hepatitis B virus infections (Monroe and Jones, 1977). This cutaneous reaction may result from the generation of anaphylatoxins by antigen-antibody complement activation and subsequent tissue mast cell stimulation. Infestation with the itch mite, Sarcoptes Scabei var. hominis (scabies) also has been reported to provoke a generalized urticarial reaction (Falk and Bolle, 1980; Chapel et al., 1981). The diagnosis of scabies infection should be suspected in urticarial patients who have papules or papulovesicles in the interdigital folds, intertriginous areas and/or around the nipples and umbilicus and give a history of intense nocturnal pruritus. Parasitic organisms with a tissue invasion phase such as Strongyloides, Ascaris and Toxocara have been implicated in causing chronic urticaria. Historically, focal bacterial, fungal, and yeast infections frequently have been suggested as etiologic agents in patients with chronic urticaria to the extent that evaluations for infections in the paranasal sinuses, teeth, gums, tonsils, gallbladder and genitourinary tract have been advocated. In a study of 106 patients with chronic urticaria/angioedema evaluated for an infectious cause, 78 were found to have some form of chronic infection; however, only four improved following therapy (Rorsman, 1962). Therefore, although important to consider as potential cause, focal infections may be less commonly linked to chronic urticaria reactions than has been previously reported.

Insect Bites and Stings

Urticaria and angioedema may result from a local allergic response to stings by Hymenoptera. In addition, fire ants, deer flies, black flies, mosquitos and kissing bugs (Triatoma protracta) may provoke similar localized reactions. An augmented cutaneous response to insect bites has been termed "Papular Urticaria". This reaction pattern has been observed primarily in

children and frequently is associated with flea bites, although other insects also may be implicated. Initially, an urticarial wheal appears which is followed in several hours by a papule or vesicle. Usually individual lesions have a central punctum indicating the site of epidermal disruption. The lesions are extremely pruritic and frequently localized to exposed areas. Unlike classic urticarial reactions, these lesions resolve over days to weeks (Blank et al., 1950). Histologically, lesions of papular urticaria show both intracellular and intercellular epidermal edema and a mixed cellular infiltrate consisting of mononuclear cells and variable numbers of eosinophils around both superficial and deep dermal vessels. The anatomical location of the lesions and the histopathologic changes described help to differentiate this disorder from other urticaria eruptions.

Physical Urticarias

Physical urticarias represent a group of disorders resulting from exposure to heat, cold, pressure, light and water. Collectively, these physical agents are the most common identifiable cause of chronic urticaria. Except for the familial forms, they tend to occur and remit spontaneously as do urticarial reactions from other etiologies. However, some patients with physical urticarias may have their disorder may persist for many years.

CHOLINERGIC URTICARIA: This urticarial response is provoked by heat, exercise and/or emotion, and characteristically appears as 1-2 mm pruritic, papular wheals surrounded by large areas of erythema (Grant et al., 1935). Typically the lesions first appear on the neck and upper thorax, and gradually spread to involve the face, back and extremities. Eventually the lesions increase in size and appear as larger urticarial plaques and sometimes angioedema. Associated pulmonary involvement manifested clinically by wheezing and documented by increased airway resistance has been reported in some patients with cholinergic urticaria (Soter, et al., 1980). Fortunately, the vast majority of patients with this disorder do not have significant pulmonary or other systemic symptoms. Studies of mast cell mediator release during attacks of cholinergic urticaria frequently have demonstrated elevated levels of plasma histamine. In addition, the release of both eosinophilic and neutrophilic chemotactic factors has been documented in these patients (Soter et al., 1980). Cholingeric urticaria is frequently seen in patients between the ages of 15 and 25 years, and has a mean duration of approximately 7.5 years (range 3 to 16 years) (Champion et al., 1969; Grant, 1936). The diagnosis of cholinergic urticaria usually can be established by history alone, i.e., an urticarial reaction pattern associated with heat, exercise and/or emotion. This can be confirmed clinically by having the patient take hot bath or exercise until sweating is induced. The intradermal administration of methacholine resulting in the development of satellite wheals around the injection site is considered a positive response in patients with cholinergic urticaria. However, this cutaneous reaction occurs in only one-third of the subjects tested (Kaplan, 1984). A subset of patients with exercise-induced urticaria have been described who experience their symptoms only in a cold environment. These patients have been described as having cold-induced cholinergic urticaria (Kaplan and Garofalo, 1981).

COLD-INDUCED URTICARIA: An urticarial response precipitated by cold exposure represents a unifying theme for at least six different disorders (Table VIII). The most common form of cold urticaria is the acquired, idiopathic type which is manifested clinically as whealing papules and plaques after minutes of cold exposure (i.e., cold air, foods, liquids, or ice). Deeper angioedematous lesions also may develop which are often painful and longer lasting. Rarely, systemic symptoms such as headaches, wheezing and syncope may occur. Elevated levels of histamine, high and low molecular weight ECF-A, and NCF-A have been demonstrated in the peripheral circulation of patients with active cold urticaria (Kaplan, et al., 1975; Wasserman et al., 1982; Wasserman et al., 1977). In addition, a recent study has reported a biphasic rise in platelet factor 4 (PF4) in three out of five patients with cold-induced urticaria (Wasserman and Ginsberg, 1984) suggesting a possible role for mast cell-derived platelet activating factor (PAF) in this disorder. Passive transfer of cold urticaria to the skin of a normal recipient has been documented in some patients with this disorder (Houser et al., 1970). Acquired cold urticaria also has been reported in patients with infectious mononucleosis, syphilis, cryoglobulinemia and cryofibrinogemia (Mathews, 1983). Two forms of dominantly-inherited, familial cold urticaria have been identified, and include individuals who have either an immediate or delayed reaction to cold exposure (Tindall et al, 1969; Soter, et al., 1977). The immediate reaction often is associated with systemic symptoms (fever, arthralgia, abdominal pain) with a concomitant leukocytosis while delayed reaction cold-induced urticaria usually is manifested by localized angioedema 9 to 18 hours after cold exposure. Patients developing urticaria occurring while exercising in the cold and cold-dependent dermographism also have been reported. Individuals experiencing cold-induced urticaria should be cautioned about sudden immersion in cold water while swimming since anaphylaxis could potentially occur under such circumstances (Mathews, 1983).

TABLE VIII

Cold-Induced Urticarial Syndromes

Idiopathic cold urticaria
Cold urticaria associated with cryoglobulins and other proteins
Delayed cold urticaria
Cold-induced "cholinergic" urticaria
Systemic cold urticaria
Cold-dependent dermographism

PRESSURE-INDUCED URTICARIA: An immediate form of pressure-induced urticaria is present in approximately 5% of the general population and is manifested clinically as dermographism (Kirby et al., 1971). Classic dermographism results in a whealing response following pressure of 4900 gm/cm^2. Many patients are asymptomatic while others experience pruritus with their dermographic response. Dermographism often accompanies other urticarial reactions. A more significant clinical manifestation of pressure-induced urticaria is seen in the delayed-onset form. Patients with this disorder develop urticaria and/or angioedema four to eight hours after local trauma, such as hammering nails, walking or running distances, or prolonged periods of sitting. Frequently, the lesions are described as burning or stinging. Pruritus usually is not present. The lesions resolve after 24 to 48 hours. Some patients experience fever, headache, chills and arthralgias accompanying their cutaneous reactions. In a study of 40 patients with delayed-pressure urticaria (DPU), 58% were noted to have these systemic symptoms while 71% and 33% were observed to have an elevated erythrocyte sedimentation rate and a peripheral blood leukocytosis, respectively (Table IX, Czarnetzki et al, 1984). Cutaneous biopsies of DPU lesions demonstrate primarily a mononuclear cell infiltrate with a few eosinophils surrounding both superficial and deep dermal vessels. Mast cell degranulation is frequently evident (Czarnetzki et al., 1985). A central role of the mast cell in this cutaneous eruption has been suggested by the observation that DPU lesions fail to arise after an appropriate stimulus in cutaneous sites depleted of mast cell mediators by the secretagogue compound 48/80 (Ryan et al., 1968). Delayed pressure urticarial responses and late-phase reactions (LPR) have several similar characteristics. Each may have an acute wheal and flare response followed 6 or more hours later by an erythematous, slightly painful eruption. Histologically, these lesions appear quite similar and both have evidence for mast cell mediator release as the primary factor in their pathogenesis (Table VI). Although the etiology of this physical urticarial reaction is unknown, a recent report has implicated a role for foods in some patients. Davis and coworkers studied six patients with DPU, and in five demonstrated a significant wheal and flare response to one or more foods (chocolate, corn, peanut, pork, Baker's yeast, sunflower, beef and shrimp). Interestingly, all five patients developed a LPR to at least one food allergen that was similar in intensity to their DPU reactions. With fasting, the ability to provoke DPU responses resolved in each patient, and returned after oral challenge with the appropriate food allergen. This study provides an additional link between LPRs and delayed-pressure urticaria. More conventionally, the diagnosis of pressure urticaria can be established by placing two 15 pound weights attached to a rope over the shoulder area for up to 15 minutes. Four to eight hours after testing, the appearance of an erythematous, poorly-defined lesion(s) at the site of pressure confirms the diagnosis.

TABLE IX

	Mean ± 1 s.d.	Range
A. Age at onset (years)	34 ± 10	19–54
Duration (years)	6 ± 8	0·3–39
Delay until onset of lesions (h)	4·5 ± 2·0	1–10
Duration of lesions (h)	20 ± 8	2–30
	Percentage of all patients	
B. Systemic symptoms	58	
Leukocytosis (> 10,000/mm³)	33	
Eosinophilia (> 300/mm³)	0	
Elevated ESR	71	
Coexistent dermographism	63	
Coexistent chronic urticaria	31	
Reaction to parabens and analgesics	44	
Atopic personal history	6	
Atopic family history	13	

Summary of important clinical and laboratory features of twelve female and twenty male patients with PU

SOLAR URTICARIA: Exposure to sun or artificial light results in an acute whealing reaction in patients with solar urticaria. The wheals usually resolve within 30 to 60 minutes but may be more prolonged in some patients. Generalized cutaneous whealing has been associated with pulmonary symptoms and syncope. Five different groups of solar urticaria patients have been described and are classified according to their reactivity to different wavelengths of light (Table X). Patients with solar urticaria must be differentiated from individuals with erythropoietic protophorphyria (EPP). In this autosomal dominant disorder, the sensation of stinging and burning occurs within minutes of sunlight exposure. Unlike those with solar urticaria, EPP patients have persistent cutaneous lesions that result in significant acne-like scars in sun-exposed areas. The presence of solar urticaria can be established by provoking a whealing response with the appropriate wavelength of light to which the patient is sensitive. Although the mechanism is not well-defined, positive passive transfer studies have been reported in patients with Type I and IV solar urticaria (Harber et al., 1963).

TABLE X

Solar Urticaria Subgroups

Patient Subgroup	Spectra of Light Sensitivity (nm)
I	285-320 (PT)*
II	320-400
III	400-500
IV	400-500 (PT)
V	280-500

* positive passive transfer

AQUAGENIC URTICARIA: In this extremely rare condition, exposure to tepid water results in small 1-2 mm wheals with surrounding large areas of erythema in patients with aquagenic urticaria (Shelley and Ravonsley, 1964). The diagnosis is established by exposing the skin of patients to a towel soaked in water at room temperature for fifteen minutes. Because "densensitization" may occur with repeated water exposure, the patient must avoid bathing for 72 hours prior to testing. Recently a similar condition has been reported in individuals who suffer from water-induced pruritus (aquagenic pruritus) (Steinman and Greaves, 1985). It is conceivable that such patients are experiencing a "subclinical" form of aquagenic urticaria.

Contact Urticaria

Contact urticaria is characterized by transient, localized whealing associated with surrounding erythema elicited by the contact of skin or mucous membranes with a particular substance. Within the past 10 years, agents capable of inducing this local skin response have attracted a great deal of interest. Two different mechanisms are now recognized (immunologic and nonimmunologic) by which contact urticaria may be elicited (Von Krogh and Maibach, 1981). The wheal and flare response of contact urticaria usually is evident within 30 to 60 minutes after exposure to the eliciting substance, and as in other urticarial reactions, resolves within 24 hours. Unlike the delayed- in-time eruption of contact dermatitis, there is no clinical evidence of epidermal alteration (vesiculation or scaling); however, as is frequently seen in lesions of contact dermatitis, this urticarial response may assume a geometric configuration. These clinical features are useful in differentiating contact urticaria and differentiating this cutaneous eruption from contact dermatitis. Although the initial skin reaction of contact urticaria always occurs at the site of contact, some patients also experience systemic symptoms including: generalized urticaria, wheezing, laryngospasms, abdominal cramping and rarely anaphylaxis. The principle mechanism for immunologic contact urticaria is believed to be mediated by antigen-specific IgE antibodies; (Table XI) however, there have been relatively few convincing reports in which specific IgE antibodies have been identified (Pigatto et al., 1983; Agrup and Siostedt, 1985). In a study of 101 randomly-selected laboratory technicians working with animals, 14 were demonstrated to have contact urticaria. All fourteen were clinically sensitive to rats, 7 had urticaria after handling mice, and 4 developed itching and redness after contact with guinea pigs. In 10 subjects, contact with the animals' tail alone resulted in a localized cutaneous reaction. Skin testing to rat allergen provoked a wheal and flare reaction in 13 of the 14 patients. In cases of nonimmunologic contact urticaria, erythema and mild edema develop within 60 minutes of contact with the provocative substance. Usually the patient experiences varying degrees of burning, stinging and/or itching. In some instances, these symptoms arise in the absence of significant cutaneous changes. Localized and systemic manifestations of mast cell mediator release have been described in women using cosmetic preparations. Contact urticaria, generalized urticaria, rhinitis, asthma, and syncope have occurred in women during the application of the hair bleaching reagent, ammonium persulfate. This chemical is a common constituent of hair bleaches, but also is widely used in industrial processes as an oxidizing agent (pharmaceutical metal, textile, photography, food preservation, cellophane, rubber and adhesives, and paper).

To date passive transfer studies have been negative; however, ammonium sulfate appears to be a mast cell degranulator in a select population (Fisher and Dooms-Goosens, 1976). The presence and magnitude of a contact urticarial reaction appears to be dependent on multiple factors including: the physical properties of the substance, its concentration at the site of application, the vehicle in which the substance is suspended, and the anatomical site exposed. A broad range of substances have been reported to induce both immunologic and nonimmunologic contact urticaria. These are listed in Tables XI-XII. Benzoic, sorbic and cinnamic acids and cinnamic aldehyde are among the most commonly reported etiologic agents of contact urticaria.

FOODS
- Dairy products
  - Cheese[66]
  - Egg[43, 139, 147]
  - Milk[33]
- Seafood
  - Cod[58]
  - Fish[5, 58, 66, 90]
  - Prawns[116]
  - Shrimp[112]
- Fruits
  - Apple[31, 71, 79, 107, 127]
  - Apricot[57]
  - Banana[107, 121]
  - Kiwi[170]
  - Mango[121]
  - Orange[21]
  - Peach[90, 167]
  - Plum[167]
- Grains
  - Flour[66, 92]
  - Malt (beer)[157]
  - Wheat bran[84]
- Honey[90]
- Nuts[121]
  - Peanut butter[99]
  - Sesame seed[121]
  - Sunflower seed[121]
- Meats
  - Beef[31, 42]
  - Chicken[3]
  - Lamb[92]
  - Liver[45]
  - Turkey[92]
- Spices[66, 120]
- Vegetables
  - Beans[121]
  - Cabbage[17]
  - Carrot[31, 60, 71, 107]
  - Celery[46, 60, 71]
  - Chives[66]
  - Cucumber[66]
  - Endive[78]

FOODS *(Continued)*
- Garlic[66]
- Lettuce[48, 78]
- Onion[60, 66]
- Parsley[60]
- Parsnip[60, 71]
- Potato[25, 31, 60, 71, 85, 107, 117, 125]
- Rutabaga (swede)[60, 71]
- Soybean[121]
- Tomato[60, 66, 71]

FRAGRANCES AND FLAVORINGS
- Balsam of Peru[147]
- Benzoic acid[165]
- Menthol[124]

MEDICAMENTS
- Antibiotics
  - Ampicillin[126]
  - Bacitracin[24, 136]
  - Cephalosporins[153]
  - Chloramphenicol[77]
  - Gentamicin[103]
  - Iodochlorhydroxyquin[164]
  - Neomycin[103]
  - Penicillin[10, 61, 103]
  - Streptomycin[87, 140]
- Mechlorethamine[27, 54]
- Phenothiazines
  - Chlorpromazine[61]
  - Promethazine[40]
- Pyrazolones
  - Aminophenazone[20, 104]
  - Methamizole[104, 144]
  - Propylphenazone[104]

METALS
- Nickel[110, 123]
- Platinum[43, 86]
- Rhodium[43]

ORGANISMS, TISSUES, FLUIDS, SECRETIONS
- Blood[43, 44, 56]
- Cockroaches[171]
- Dander[38, 143, 129]
- Gut[114]

ORGANISMS, TISSUES, FLUIDS, SECRETIONS *(Continued)*
- Hair[15, 44, 128]
- Liver[72]
- Placenta, amniotic fluid[43, 145]
- Saliva[16, 154]
- Seminal fluid[6, 22, 59, 87, 97]
- Silk[138]
- Spider mite[133]

PLANT SUBSTANCES
- Algae[21]
- Birch[81]
- Cotoneaster[156]
- Henna[26]
- Lichens[21]
- Mahogany[54]
- Rubber latex[51, 53, 75, 106, 122]
- Teak[112]

PRESERVATIVES AND GERMICIDALS
- Benzyl alcohol[32]
- Butylated hydroxytoluene[123]
- Chloramine[29]
- Formaldehyde[62, 89, 105]
- Parabens[64]
- Phenylmercuric proprionate[102]
- Polysorbate[60, 93]
- Sodium hypochlorite[119]
- Sorbitan monolaurate[11]

MISCELLANEOUS
- Alcohols
  - Amyl[135]
  - Butyl[135]
  - Ethyl[39, 135]
  - Isopropyl[39, 135]
- p-Aminodiphenylamine[164]
- Benzophenone[130]
- Carbonless copy paper[96]
- Citraconic anhydride[68]
- Denatonium benzoate[8]
- Diethyltoluamide[94, 109, 159]
- Epoxy resin[169]

MISCELLANEOUS *(Continued)*
- Lanolin alcohol[164]
- Oleylamide[123]
- Patent blue dye[70]
- Perlon (synthetic fiber)[115]
- Phosphorus sesquisulfide[13, 168]
- Polyethylene glycol[37]
- Potassium ferricyanide[69]
- Sodium silicate[146]
- Terpinyl acetate[105]
- Vinyl pyridine[139]
- Zinc diethyl-dithiocarbamate[63]

Table XI.

Substances capable of causing immunologic contact urticaria.

FOODS:
- Fish[44]
- Spices
  - Cayenne pepper (capsicum)[7, 35]
  - Thyme[35, 132]

FRAGRANCES AND FLAVORINGS:
- Balsam of Peru[35, 40, 47, 49, 65, 79, 98, 132, 137]
- Benzaldehyde[46]
- Cassia (cinnamon) oil[134, 137]
- Cinnamic acid[78, 98]
- Cinnamic aldehyde[74, 98, 118]
- Menthol[35, 132]
- Vanillin[137]

MEDICAMENTS (INCLUDING RUBEFACIENTS):
- Alcohols
  - Ethyl[35, 79, 132]
  - Butyl[79]
- Benzocaine[141]
- Camphor[35, 132]
- Cantharides[35, 132]
- Capsaicin[7]
- Chloroform[35, 132]
- Dimethylsulfoxide[50, 76]
- Friar's balsam[35, 132]
- Methyl salicylate[35, 132]
- Mustard (black)[35, 132]
- Myrrh[35, 132]
- Nicotinic acid esters
  - Benzyl[2]
  - Methyl[154]
  - Tetrahydrofurfuryl[151]
- Tar extracts[35, 132]
- Tincture of benzoin[35, 132]
- Thyme oil[35, 132]
- Witch hazel[35, 132]

METALS:
- Cobalt[145]

ORGANISMS, TISSUES, FLUIDS, SECRETIONS:
- Arthropods[38]
- Caterpillars[38, 67]
- Jellyfish[38]
- Moths[38]
- Stinging insects[38]

PLANT SUBSTANCES:
- Coral[38]
- Nettles[38]
- Sea anemone[38]

PRESERVATIVES AND GERMICIDALS:
- Benzoic acid[23, 79, 98]
- Formaldehyde[1]
- Sodium benzoate[79]
- Sorbic acid[23, 79, 98, 134]

MISCELLANEOUS:
- Acetic acid[79]
- Butyric acid[79]
- Pine oil[35, 132]
- Resorcinol[35, 132]
- Turpentine[35, 132]

Table XII. Substances capable of causing nonimmunologic contact urticaria.

Acetylsalicylic acid[33]*	Lindane[73]*
Acrylic monomer[33]*	Monoamylamine[149]
Aliphatic polyamines[73]*	Nail polish[40]*
Aminothiazole[73]	Perfume[40]*
Ammonia[113]	Plastic[111]
Ammonium persulfate[12, 18, 36]	
Benzoyl peroxide[152]	Polysorbate 80[19]
Castor bean pomace[73]	Rouge[28]
Estrogen cream[40]*	Sodium sulfite[38]*
Hair spray[40]*	Sulfur dioxide[125]
Horse serum[40]*	Wool[38]*

Table XIII. Substances capable of causing contact urticaria by uncertain mechanisms.

The diagnosis of contact urticaria can be accomplished by patch testing the patient to the agents in question. Initial testing can be performed using the "open test" method. The substance is applied to the skin and the site is observed for a wheal and flare reaction over the ensuing 30 to 60 minutes. If no response is elicited, then the material is reapplied and occluded to enhance penetration. After 30 and 60 minutes the site is examined for a localized urticarial response. It should be cautioned that such testing procedures have provoked anaphylactoid reactions in patients with contact urticaria (Table XIV).

AGENT	TESTING METHOD
Aminophenazone[20]	Patch
Bacitracin[24]	Intradermal
Balsam of Peru[147]	Patch
Chloramphenicol[77]	Patch
Diethyl meta-toluamide[109]	Open
Egg[148]	Intradermal
Epoxy resin[109]	Patch
Mechlorethamine[27]	Open
Mechlorethamine[54]	Intradermal
Neomycin[103]	Patch
Penicillin[103]	Patch
Streptomycin[87]	Intradermal

*Modified from von Krogh, G., and Maibach, H. I.: The contact urticaria syndrome—1982. Semin. Dermatol., *1*:59–66, 1982.

Table XV. Documented cases of anaphylactoid reactions to cutaneously tested agents

URTICARIA ASSOCIATED WITH SYSTEMIC DISEASES

The association of urticaria with underlying systemic diseases is relatively uncommon although this cutaneous reaction pattern has been linked to some disorders (Table XV). In most instances the mechanism for urticaria is unknown. Urticarial lesions have been reported to occur in 7 to 22 percent of the patients with systemic lupus erythematosus (SLE) (Tuffanelli and DuBois, 1964; O'Loughlin et al., 1978). In some cases, these lesions demonstrate histologically the typical changes of urticaria, while in others there is evidence of leukocytoclastic vasculitis. As discussed in a previous section, some patients with essential mixed cryoglobunemia may initially present with urticarial lesions following cold exposure. However, the presence of palpable purpuric lesions, Raynaud's phenomenon and cutaneous ulcerations help to distinguish these patients from those with uncomplicated chronic urticaria. Most patients with serum sickness develop an urticarial reaction pattern early in their disease course. Histologically these lesions may demonstrate typical changes of urticaria or may show more significant inflammation in the form of vasculitis (Kohler, 1983). Urticarial-like papules and plaques also have been reported in children with juvenile rheumatoid arthritis; however, unlike common hives, these lesions characteristically are non-pruritic (Calabro and Marchesano, 1968). Lesions of acute and chronic urticaria have been identified in patients with both hypothyroidism and hyperthyroidism (Pace and Garrett, 1975). We recently observed a patient with urticaria of one year duration who was maintained on oral thyroid replacement following a total thyroidectomy. Her cutaneous eruption had been unresponsive to multiple therapeutic regimens. At the time of presentation to us, the patient was both clinically and chemically

hyperthyroid while being treated with thyroid extract replacement. Her medication was switched to a lower dosage of Synthroid. One month later, she remained hyperthyroid and her hives persisted; her Synthroid dosage was reduced further. Concommitant with becoming euthyroid, her urticarial eruption completely resolved. The patient refused a diagnostic rechallenge of a higher thyroid replacement dosage. Urticaria and angioedema also have been reported in patients with lymphomas and visceral carcinomas although these cutaneous markers of malignancy appear to be rare (Urbach, 1942). Patients with both systemic and isolated cutaneous mastocytosis may have spontaneous urticarial lesions; however, these arise in foci of cutaneous mast cell infiltrates which can be readily distinguished clinically. Bouts of urticaria and angioedema have been described in adolescents who have an autosomal dominant disorder originally described by Muckle and Wells (1962). These children develop an urticarial eruption precipitated by heat exposure or emotions that may be accompanied by chills and malaise. Progressive nerve deafness and amyloidosis of the kidney develop after a variable period of time (Muckle and Wells, 1962; Black, 1969).

TABLE XV

SYSTEMIC DISEASES ASSOCIATED WITH AN URTICARIAL ERUPTION

Systemic lupus erythematosus
Mixed cryoglobulinemia
Serum sickness
Juvenile rheumatoid arthritis
Hyperthyroidism
Hypothyroidism
Neoplasms
Mastocytosis
Muckle-Wells Syndrome

Pruritic Urticarial Papules and Plaques of Pregnancy (PUPP).

PUPP is a pruritic eruption associated with pregnancy that was originally described by Lawley and his associates (1979). Characteristically, patients with this disease develop erythematous urticarial plaques and papules during the last trimester of pregnancy. Initially these lesions begin centrally over the abdomen and extend to involve the thighs, buttocks and distal extremities. The facial area is usually spared. In some patients, only the lower extremities are involved. Despite the highly pruritic nature of this urticarial reaction, cutaneous excoriations are rarely observed.

Skin biopsies of lesional tissue show histologic changes similar to those observed in other urticarial reactions. The epidermis is usually normal although some evidence of intraepidermal cell edema (spongiosis) may be evident. Superficial dermal edema and perivasculature infiltrates consisting predominantly of lymphocytes and histiocytes are most commonly observed. Variable numbers of eosinophils infiltrating the dermis also have been described. Direct immunofluorescence studies of involved skin looking for immunoglobulin and complement deposition have been negative (Lawley et al., 1979; Callen and Hanno, 1981). Although directly associated with pregnancy, the underlying pathophysiology of this disorder is unknown. Clinically, it appears that the cutaneous mast cell plays an important role in the pathogenesis of PUPP.

Management of patients with this disorder consists of oral antihistamine therapy for the pruritus in combination with either topical or oral corticosteroids. Overall, of the twenty-two patients reported in two different studies, only three required oral corticosteroid therapy (Lawley et al., 1979; Callen and Hanno, 1981). The prognosis for the patient and the fetus appears to be excellent. The maternal cutaneous lesions usually resolve shortly after delivery and no associated abnormalities or adverse reactions have been reported in infants from mothers with PUPP. Patients who develop PUPP are not necessarily at risk for a recurrence during a second pregnancy. Callen and Hanno described two PUPP patients who failed to develop this disorder with subsequent pregnancies. Because of its benign course and good prognosis, PUPP should be distinguished from several other pruritic dermatoses of pregnancy which have been associated with increased maternal and fetal morbidity and mortality (Table XVI). Furthermore, the PUPP syndrome needs to be distinguished from other disorders, such as urticaria and erythema multiforme that also may occur during but are not related to pregnancy.

*Comparative Features of the Dermatoses of Pregnancy**

	PUPPP	Herpes gestationis	Pruritus gravidarum	Papular dermatitis of pregnancy	Prurigo gestationis	Impetigo herpetiformis
Onset & incidence	Last trimester; becoming common	Second trimester; rare	Last trimester; common (0.02–2.4%)	Throughout pregnancy; rare	Second half of pregnancy; common	Second half of pregnancy; rare
Distribution	Abdomen with spread to extremities; striae involved; face spared	Generalized—buttocks, abdomen, extremities, mucous membranes	Abdomen, trunk, extremities	Generalized; face involved	Trunk and extensor extremities	Intertriginous zones & thighs
Clinical lesions	Erythematous papules and urticarial plaques; excoriations rare	Erythematous papules, vesicles & bullae	No primary lesions; excoriations	Erythematous papule, often topped by firmer sloping papule; excoriation and secondary crust common	Erythematous papules, round dermatitic plaques, urticarial lesions†	Small, sometimes-coalescent pustules
Histology	Spongiotic dermatitis with superficial mixed perivascular inflammation	Subepidermal bullae often containing eosinophils	Nonspecific cholestasis of liver; no skin biopsy data	Incomplete data	No data	Spongioform & intraepidermal pustule‡
Immunofluorescence	Negative	IgG, IgA, IgM, Clq, C_3 of basement membrane in perilesional skin; circulating HG factor	NA	NA	NA	NA
Laboratory abnormalities	None	Peripheral blood eosinophilia	↑ bile acid; abnormal liver functions (variable);	↑ hCG?; ↓ plasma hydrocortisone; ↓ urinary estriol?;	None	Hypocalcemia, leukocytosis; systemic steroids
Treatment	Topical steroids; systemic steroids if necessary	Systemic steroids	topical antipruritics, cholestyramine	systemic steroids	Topical antipruritics	
Complications	None except similar neonatal eruption reported[3]	Maternal: 2° infection; fetal: ↑ prematurity & stillbirth; blisters in neonate	Maternal: none; fetal: ↑ prematurity	Maternal: none; fetal: ? ↑	None	Maternal: prostration; renal failure; cardiac failure; fetal: ↑ abortion, stillbirth, neonatal death
Prognosis	Variable	Recurrences common in subsequent pregnancies	Recurrences common in subsequent pregnancies	Recurrences common in subsequent pregnancies	Recurrences uncommon[16]	

*Autoimmune progesterone dermatitis is excluded because only one case report has been published.
†May be part of the PUPPP syndrome.
‡May be pustular psoriasis exacerbated by pregnancy.

Table XVI

Urticarial Vasculitis

The term "urticarial vasculitis" has evolved from the original report of McDuffie, Sams, and coworkers (1973), who described four patients with an idiopathic disorder that consisted of intermittent episodes of arthritis, persistent hypocomplementemia , and recurrent urticaria-like lesions which histologically demonstrated changes of leukocytoclastic vasculitis. In addition, two of these patients had evidence of active renal involvement. Although each patient appeared to have a disorder similar to systemic lupus erythematosus (SLE), all lacked the specific diagnostic criteria for this

disease. Over the last ten years a number of reports have evolved describing patients with urticaria-like lesions that on biopsy show changes of necrotizing vasculitis. In some of these individuals an underlying disorder has been documented. Diseases such as serum sickness, SLE, Sjogren's syndrome, viral hepatitis, infectious mononucleosis, and essential cryoglobulinemia have been associated with vasculitic, urticaria-like skin lesions. Other patients however, like those described by McDuffie and associates, appear to have a unique clinical syndrome that is distinct from the above mentioned diseases (Agnello et al., 1975; Soter, 1977; Zeiss et al., 1980). It is this latter group of patients with (idiopathic) urticarial vasculitis that will be the focus of this discussion.

Patient Population: Idiopathic urticarial vasculitis appears to be more prevalent in women. In a series of sixteen patients, Soter noted a female to male ratio of 7:1 (3) (Table XVII); Sanchez and coworkers (1982) also reported a female predominance (2:1) in their review of 40 patients. The mean age of disease onset is approximately 40 years (range of 18 to 85 years) with disease duration ranging from 1 month to 25 years. The diagnosis of idiopathic urticarial vasculitis is based on a combination of clinical and laboratory findings. No single physical sign or serologic test is pathognomonic for this syndrome; however, certain symptoms and signs may be valuable in differentiating patients with this disorder from those with other immune complex diseases or uncomplicated urticaria.

TABLE XVII

Clinical and Laboratory Features in Patients with Urticarial Vasculitis

(Soter)

Features	Patients with Hypocomplementemia	Patients with Normocomplementemia	Normal Values
No. of patients	7	9	
Sex (M/F)	2/5	0/9	
Age (yr)	38 (21–61)	40 (25–68)	
Duration episodes of skin lesions (yr)	2.1 (4 mo–5 yr)	12.3 (3 mo–25 yr)	
Erythrocyte sedimentation rate (mm/hr)	53 (28–92)	38 (4–66)	
Immunoglobulins:			
IgG (mg/ml)	12.6 (7.9–20.0)	10.0 (5.9–15.5)	8.6 (5.4–12.5)
IgM (mg/ml)	2.9 (0.9–12.0)	1.5 (0.8–2.3)	0.9 (0.3–2.2)
IgA (mg/ml)	2.9 (0.9–6.6)	3.4 (1.3–7.5)	2.6 (1.1–5.0)
IgD (μg/ml)	25 (11–42)	30 (11–45)	20 (10–135)
IgE (IU/ml)	89 (10–160)	56 (10–180)	87 (0–357)

*All data are expressed as mean levels; ranges are given in parentheses; normal values (±2 SD) based on analysis of 100–500 randomly selected healthy subjects.

Symptoms: Recurrent, pruritic, urticaria-like lesions are the most common complaint among patients with this disorder, and are usually the primary reason for seeking medical attention. Soter reported that fourteen of his sixteen patients noted pain or pruritus with the onset of their skin eruption. Sanchez and coworkers also reported that lesional itching and burning was a frequent symptom in their patients. Joint pain and stiffness is another common symptom among these patients. Joint tenderness is often transient, lasting less than 72 hours, and usually paralleling skin disease activity. Involvement of the hands, elbows, ankles, and knees has been observed most frequently. Gastrointestinal (GI) symptoms including abdominal pain, nausea, vomiting, and diarrhea have been temporally associated with skin and joint involvement. In their original report, McDuffie and associates noted that three of their four patients had GI-related problems; Sanchez et al. also reported that at least 25% of their patients experienced nausea, vomiting and/or abdominal pain. Other symptoms encountered less frequently in patients with the idiopathic form of urticarial vasculitis include recurrent headaches, eye pain, and associated chest pain (Table XVIII). Thus, the symptom complex of burning or painful urticarial lesions associated with joint and/or gastrointestinal complaints should alert the clinician to consider the diagnosis of urticarial vasculitis.

TABLE XVIII
Clinical Findings in Forty Patients
With Urticarial Vasculitis

(Sanchez et al.)

Symptoms and signs	Hypocomplementemic (N = 16)	Normocomplementemic (N = 24)
Pruritus	5	16
Arthralgia	12	9
Arthritis	9	2
Genitourinary (hematuria, proteinuria)	10	4
Abdominal or chest pain	5	5
Pulmonary*	9	3
Uveitis, episcleritis	6	1
Neurologic (pseudotumor cerebri)	2	1
Gastrointestinal (nausea, vomiting)	5	4
Fever	2	4
Raynaud's	1	1
Cardiac	1	0

*Chronic obstructive pulmonary disease in seven.

Cutaneous Signs: The cutaneous lesions most frequently associated with this disorder are reported to be "urticaria-like"; however, several subtle clinical signs may be present that differentiate this cutaneous eruption from typical urticaria. Individual lesions of urticarial vasculitis are frequently noted to persist longer than those of uncomplicated urticaria, often lasting greater than 24 hours (McDuffee et al., 1973; Soter, 1977). On careful examination, some of these vasculitic lesions may have small areas of demonstrable purpura. Purpuric foci have been most frequently observed in lesions involving the lower extremities. With resolution of individual skin lesions, secondary changes of hyperpigmentation or "staining" are sometimes detectable. In addition to hive-like lesions, several other cutaneous signs have been reported in patients with idiopathic urticarial vasculitis and include angioedema, widespread livedo reticularis, erythema multiforme-like lesions, and bullae (Agnello et al., 1975; Soter, 1977; Sanchez et al., 1980).

Systemic Manifestations: A number of patients with this syndrome have evidence of extracutaneous involvement. Arthritic changes appear to be a relatively common finding. McDuffie et al., and Zeiss and coworkers reported active joint inflammation in eight out of eight patients. In their series of forty patients, Sanchez and associates noted a 28% incidence of arthritis. In most cases the joint involvement has paralleled cutaneous disease activity. Additional signs of systemic involvement in these patients includes reports of associated fever, generalized lymphadenopathy, asthma, uveitis, episcleritis, and neurologic findings. Although neurologic involvement appears to be relatively uncommon, some patients have experienced recurrent seizures, pseudotumor cerebri, meningitis, and mononeuritis (Zeiss et al., 1980).

Serologic Parameters: A decrease in total serum complement levels has been a frequently reported finding in patients with idiopathic urticarial vasculitis. McDuffie and coworkers noted a decrease in both the early and late complement components in all four of their patients. Subsequent reports have indicated that approximately 50-60% of the patients with urticarial vasculitis will have detectable hypocomplementemia (Soter, 1977; Monroe, 1981), with most having depressed levels of the early classical pathway components. None of the patients reported with this syndrome have had evidence of abnormal C1 esterase inhibitor activity, and therefore, are readily differentiated from patients with hereditary angioedema. The basic mechanism for complement activation is unknown; however, immune complex deposition is one possible explanation. Circulating immune complexes are commonly detected in patients with idiopathic urticarial vasculitis (McDuffie et al., 1973; Zeiss et al., 1980; Sanchez et al., 1982). More recent studies also have demonstrated the presence of low molecular weight (7S) C1q precipitins in the sera of several patients. Marder and associates (1978) have partially characterized these C1q-precipitins which appear to be comprised, in part, of monomeric IgG that is bound to the first component of complement (C1q) via its Fc receptor. Not all patients with urticarial vasculitis have evidence of C1q precipitins; therefore the pathophysiologic significance of these circulating molecules remains unknown. An additional laboratory finding initially reported in this patient group was an elevated erythrocyte sedimentation rate (ESR). In more recent reports, however, a number of patients have been noted to have a normal ESR. Furthermore, in a study of patients with typical urticaria, Monroe et al., noted an elevated sedimentation in at least 29% of their patients. A few patients with urticarial vasculitis will have evidence of renal disease with persistent proteinuria

and/or microscopic hematuria being detected most commonly. When thoroughly evaluated, most of these patients have pathologic changes of active glomerulonephritis ranging in severity from a focal necrotizing disorder to a diffuse proliferative process. McDuffie et al. detected renal involvement in two of their four patients with urticarial vasculitis, while Sanchez and coworkers reported biopsy proven renal pathology in eight of their forty patients (Table XIX). Soter, however, noted active kidney disease in only one of his sixteen patients. From these and other studies it appears that patients with urticarial vasculitis are at risk for renal involvement; however, the extent of disease activity appears to be relatively mild. More recent reports have indicated that some patients with urticarial vasculitis may have an accelerated course of chronic obstructive pulmonary disease (COPD) (Schwartz et al., 1982). Although most of the patients reported with this finding have been smokers, the severity of their pulmonary involvement has been considered advanced beyond the changes expected for both their age and smoking history. In a recent report, Falk (1984) described a 45 year old woman with urticarial vasculitis associated with pleuritic chest pain and hemoptysis. An open lung biopsy demonstrated leukocytoclastic vasculitis of the pulmonary venules. Thus, this and other studies emphasizes the potentially serious systemic nature of this disorder.

Additional tests (antinuclear antibodies, antibodies to double-stranded DNA, cryoglobulins, circulating rheumatoid factor, false-positive VDRL, hepatitis B surface antigen) that are frequently employed for the diagnosis of connective tissue diseases or immune complex-mediated disorders usually are either negative or of low titer in patients with urticarial vasculitis.

Table XIX

Histological Changes on Renal Biopsies
From Eight Patients With Urticarial Vasculitis

Finding	No. of patients
Focal necrotizing vasculitis	2
Proliferative glomerulonephritis	
Focal	2
Diffuse	2*
Tubulointerstitial nephritis	1
Mesangiopathic glomerulopathy	1

*One patient was normocomplementemic.

(Sanchez et al.)

Histological Studies: The diagnosis of idiopathic urticarial vasculitis is supported in great part by the histological examination of lesional skin. In the majority of patients, the hallmarks of necrotizing vasculitis are evident and include endothelial cell swelling with fibrinoid deposits in and around the venules, perivascular leukocytic infiltrates (predominantly neutrophils) with leukocytoclasis, and red blood cell extravasation. Lesional skin biopsies from some patients however, may not demonstrate all of these characteristic pathological features. Monroe et al. have identified a group of patients with urticaria-like lesions that show less severe histologic changes of necrotizing

vasculitis. These patients frequently have normal complement levels and appear to have less significant systemic disease. Thus, the extent of the inflammatory response noted on skin biopsy may serve as a useful guideline to assessing overall disease activity in patients with urticarial vasculitis. Direct immunofluorescence (DIF) studies on lesional skin from patients with this syndrome have ranged from no detectable deposition of complement or immunoglobulins to the appearance of these immunoreactants in dermal vessels and along the dermo-epidermal junction (McDuffie et al., 1973; Soter, 1977; Sanchez et al., 1982). Interestingly, Sanchez et al., noted that seven of their patients with renal disease had IgG and IgM deposited at the epidermal-dermal basement membrane zone. Although further studies are necessary, this DIF finding may serve as a useful marker for renal involvement in patients with this syndrome. It should be emphasized that positive DIF findings in lesional skin are not specific for idiopathic urticarial vasculitis and have been demonstrated in a number of other immune complex-mediated disorders. Conversely, the failure to identify immunoglobulins and/or complement in involved skin does not exclude this diagnosis. Although the etiology of urticarial vasculitis is unknown, this disorder appears to result in part from circulating immune complex deposition and complement activation. Interestingly, patients with this syndrome manifest urticaria-like lesions, a cutaneous sign most frequently associated with mast cell stimulation and mediator release. Several lines of evidence suggest a significant role for the cutaneous mast cell in urticarial vasculitis. (1). Previous studies have indicated that the mast cell plays an important role in several different types of immune reactions, including Type I (IgE-mediated), Type III (immune complex-related), and Type IV (delayed-in-time) hypersensitivity reactions (Johnson et al., 1975; Lepow et al., 1970; Rocklin et al., 1980; Askenase et al., 1981). (2). The intradermal administration of mast cell mediators, such as histamine, prostaglandin D_2 and the leukotrienes C,D and E, provoke an erythematous whealing response (Askenase, et al., 1981). (3.) Histologic studies of urticarial vasculitic lesions have demonstrated mast cell degranulation in conjunction with leukocytoclastic changes (4). Some patients with this disorder have had at least a partial response to antihistamine therapy. From our limited understanding of the pathogenesis of urticarial vasculitis, there are several potential mechanisms that could result in mast cell degranulation. Immune complex deposition with subsequent complement activation frequently leads to the generation of the anaphylatoxins, C_{3a} and C_{5a}; both of these molecules are known potent stimulators of human cutaneous mast cells. Polymorphonuclear leukocytes, the predominant cell type in urticarial vasculitic lesions, secrete lysosomal proteins which appear capable of triggering mast cell mediator release. In addition, work in our laboratory indicates that activated lymphocytes, which also are present in lesional skin, release a molecule(s) with mast cell-stimulating capabilities. Following activation by any one of these potential mechanisms, the mast cell releases a number of preformed and newly-formed mediators, including histamine, NCF, ECF-A, PGD_2 and leukotrienes. These pharmacologically potent molecules are capable of regulating numerous physiologic and immunologic events. Thus, although the mast cell may not account directly for the pathophysiologic defect in idiopathic urticarial vasculitis, the release of its mediators may have a significant impact on the inflammatory process involving the skin and possibly other organs.

Numerous treatment modalities have been employed for patients with idiopathic urticarial vasculitis. Combined H_1 and H_2 antihistamines have been partially effective in controlling cutaneous symptoms in some patients but not

in others. Some reports have indicated a good patient response to nonsteroidal anti-inflammatory preparations and, in particular indomethacin (Sanchez, et al., 1982; Millns et al., 1980). It appears, however, that many patients with this disorder require oral corticosteroids (30-60 mg/d of prednisone) for adequate control of their disease. As an alternative, we have employed dapsone (50-100 mg/d) as a "first-line" treatment with a good therapeutic response in some patients; others however, have been relatively refractory to this medication. In patients responsive only to corticosteroids, the use of immunosuppressive agents (cyclophosphamide or azathioprine) should be considered for both their anti-inflammatory and steroid-sparing effects.

ANGIOEDEMA REACTION PATTERNS

As observed in primary urticarial reactions, a definitive cause is usually not determined for more than two thirds of the patients with chronic "giant hives" or angioedema. However, in instances where an etiologic agent can be identified, they often include the causes associated with provoking an urticarial response. This is not surprising in that nearly one half of the patients with urticaria also experience episodes of angioedema (Warin and Champion, 1974). Thus, the different etiologic factors discussed for the urticarial reaction patterns also must be considered in patients with angioedema. In addition, there are several other syndromes that should be considered when evaluating a patient with an angioedematous reaction.

Hereditary Angioedema (HAE)

Hereditary angioedema is an autosomal disorder characterized by episodic nonpruritic, painless, subcutaneous swellings lasting several hours to days. The lesions are often triggered by local trauma or emotional stress, and are usually asymmetrical. Unlike acquired angioedema, an urticarial reaction pattern is rarely present in patients with hereditary angioedema. A history of recurrent nausea, vomiting and abdominal colicky pain is common in this patient population and results from localized intestinal swelling (Pearson et al., 1972). The onset of this disorder is usually in childhood or young adulthood although it may not appear until much later (Matthews, 1983). A positive family history is usual in patients with HAE, but may not always be present. It is important to differentiate HAE from other causes of angioedema because a significant portion of patients with this disorder are at risk for laryngeal obstruction and death (Frank et al., 1976).

The underlying mechanism for HAE is a genetically determined partial deficiency of an alpha$_2$-glycoprotein termed, C_1 esterase inhibitor (C_1 INH). This protein normally inactivates the first component of complement. The absence of C1 INH results in excessive consumption of the next complement component, C_4. Thus, patients with HAE have chronically depressed levels of C_4 and during acute attacks, both C_4 and C_2 levels are depressed. In approximately 85% of the patients, C_1 INH levels are low while in the remaining 15% the protein is present in normal amounts (Frank et al., 1976; Monroe, 1983). In this latter group, the inhibitory activity of C_1 INH is abnormal; thus, a functional C_1 INH assay is necessary to correctly identify these patients.

The underlying mechanism for hereditary angioedema appears to involve both the activation of the complement and plasma kinin-forming pathways. In the absence of C_1 INH activity, the stimulation of the complement cascade proceeds essentially uninhibited following minor stimuli. Generation of the anaphylatoxins, C_{3a}, C_{4a}, and C_{5a} under such circumstances would be expected to provoke mast cell and basophil mediator release. C_1 INH also inhibits kallikrein, Hageman factor fragments and plasmin (Gigli et al., 1970; Kaplan and Susten, 1970; Schreiber et al., 1973). Following trauma, kallikrein is readily generated from high molecular prekallikrein in patients with HAE, and as a result of inadequate C_1 INH activity, it stimulates kininogen leading to the generation of bradykinin, a potent vasoactive polypeptide (Figure 8). Subcutaneous injections of either the first component of complement (C_1) or kallikrein result in angioedematous lesions in patients with HAE, suggesting a role for both complement and the plasma kinin-forming pathway (Juhlin and Michaelsson, 1969; Klemperer et al., 1968).

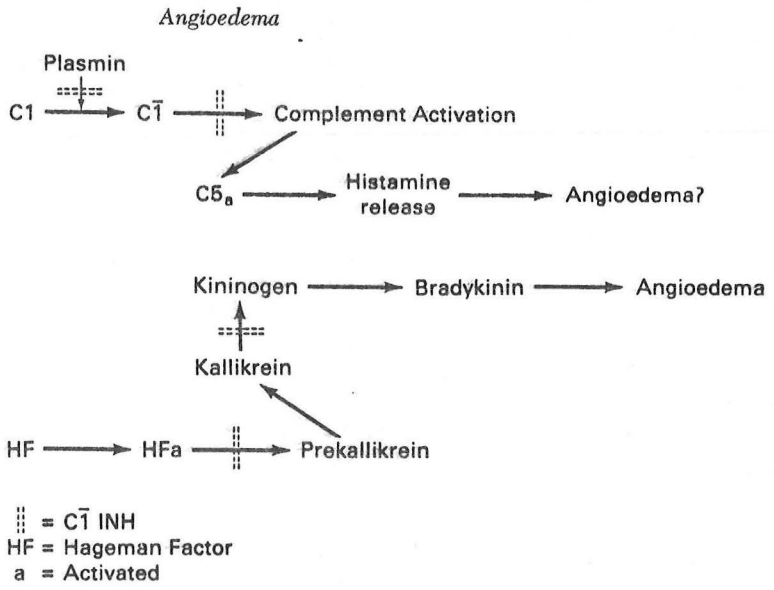


Figure 8 Activation of complement pathway and plasma kinin-forming system of intrinsic coagulation pathway that results in the development of angioedema. Note the different sites of action of C1INH in each pathway.

Patients with HAE are unresponsive to conventional antihistamine therapy and subcutaneous epinephrine injections. Attacks can be attenuated or eliminated by employing the androgens, danazol or stanozolol, which promote an increase in C_1 INH levels as well as functional activity (Gelfand et al., 1976).

Acquired C_1 INH Deficiency

Certain neoplastic disorders including lymphomas, multiple myeloma and pulmonary and colon carcinomas have been associated with a clinical syndrome similar to HAE. However, unlike HAE, these patients usually also have an urticarial reaction pattern accompanying their lesions of angioedema. As the

name implies, an acquired deficiency of C_1 INH can be detected, and is associated with a decrease of C_4 and C_2 levels. In constrast to HAE patients, however, levels of C_{1q} also are depressed (Caldwell et al., 1972; Gordon et al., 1983; Cohen et al., 1978; Ross et al., 1982).

Angioedema-Eosinophilia Syndrome

A recent report by Gleich and associates (1984) has identified a group of patients with a most unusual disorder characterized by recurrent episodes of angioedema and urticaria in association with fever, prominent weight gain and peripheral blood eosinophilia. In the four patients described, the disease onset ranged from four to 28 years of age. Severe angioedema involving all anatomical sites and persisting for up to 7 to 10 days was a prominent feature of this syndrome. An average weight gain of 14% above the normal patient weight (15 to 20 pounds) occurred within a several day period. In conjunction with these clinical features, fever was observed in 3 of 4 patients. Along with increased levels of IgM, all four patients had evidence of markedly increased levels of peripheral blood eosinophils (ranging from 2760 to 95,040). One patient also had a striking increase in his IgE level (41,920 ng/ml: normal 0.780). (Table XX). Cutaneous biopsies from lesional tissue demonstrated dermal edema, and perivascular lymphocytic infiltrates with scattered eosinophils. Despite few demonstrable tissue eosinophils, immunofluorescence staining for eosinophil granule-derived MBP was uniformly positive in each patient skin biopsy specimen. Electron microscopy studies of cutaneous lesions of tissue showed degranulation of many dermal eosiniphils and some dermal mast cells. Extensive evaluations of each patient for an underlying parasitic infection and/or antigen stimulus were negative. No patient had evidence of cardiac involvement (as has been reported in patients with hypereosinophilic syndrome). All patients responded to oral corticosteroid therapy with a resulting dramatic defervescence, diuresis and reduction in leukocyte count (Figure 9). The prognosis in these patients appears good in that two subjects have had this disorder for at least 10 years without obvious sytemic organ involvement. Because of the apparant good prognosis and dramatic response to therapy, patients with the angioedema and eosinophilia should be differentiated from those with hypereosinophilic syndrome. In addition, this disorder should be considered in the evaluation of patients with angioedema and urticaria.

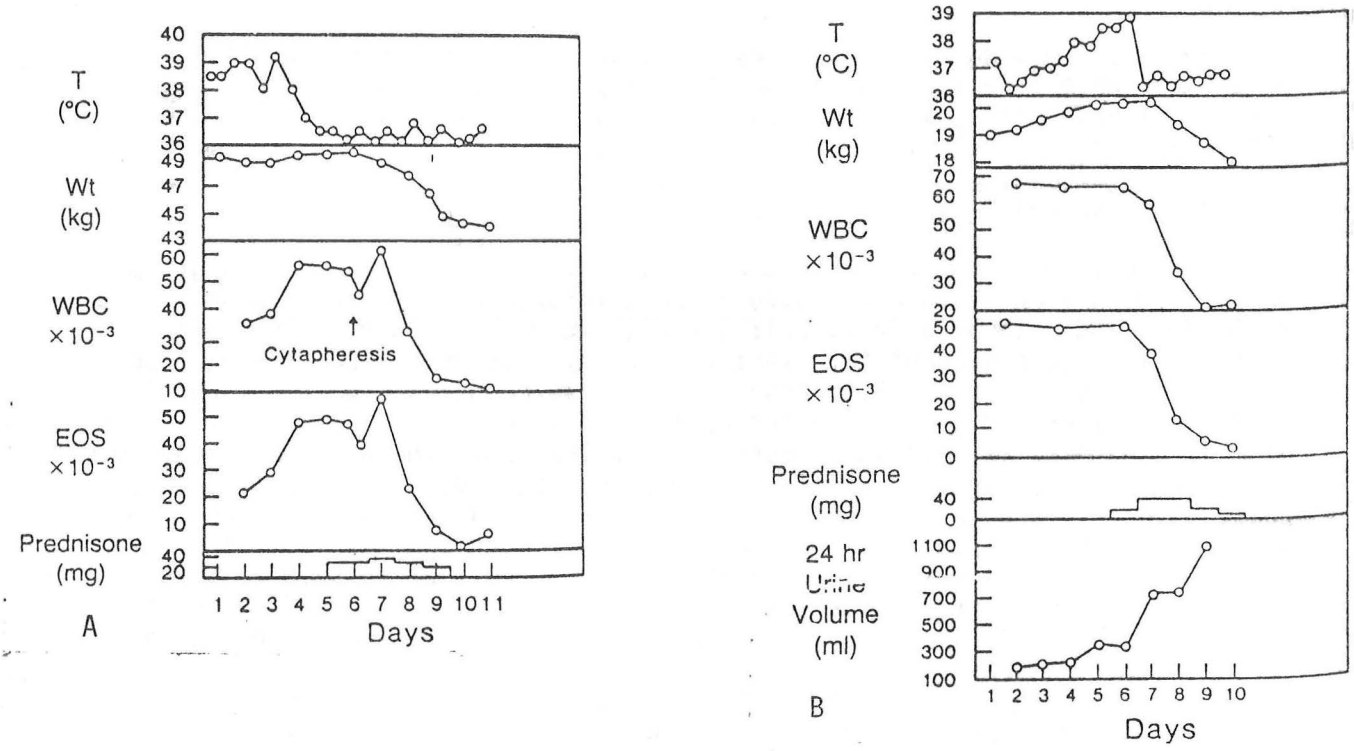


Figure 9. Clinical features during episodes of Angioedema in Patients 3(Panel A) and 4 (Panel B).

In Patient 3 the temperature spontaneously returned to normal by Hospital-Day 5. Cytapheresis on Day 6 did not affect progression of the attack. T denotes temperature, Wt weight, WBC white blood cells, and EOS eosinophils.

	Patients				Normal Values
	1	2	3	4	
Leukocytes (× $10^{-3}/\mu l$)	37.5	108	62.4	67.6	
Neutrophils (%)	11	11	2.5	12.5	
Lymphocytes (%)	12	1	6.0	11.5	
Eosinophils (%)	75	88	92	75	
Monocytes (%)	2	0	0	1.5	
IgG (mg/ml)	30.4 *	10.5	9.5	13.7	6.4–14.3
IgM (mg/ml)	8.1 *	5.1	6.7	8.3	0.2–1.4
IgE (ng/ml)	33	27	581	41,920	<780
CH_{50} (U)	48	47	29	49	41–90
C4 (ng/dl)	12	24	8	18	12–72
C3 (ng/dl)	93	178	118	169	88–252

*These are polyclonal as shown by immunoelectrophoresis.

Table XX. Laboratory data in four patients with episodic angioedema associated with eosinophilia

EVALUATION OF PATIENTS WITH URTICARIA/ANGIOEDEMA

The initial and most important approach to a patient with urticaria/angioedema is obtaining a complete history with special emphasis being placed on the recognized potential etiologic factors responsible for these reaction patterns. After this, a complete physical examination should be performed. Careful examination of the skin alone may provide important diagnostic clues. Although the lesions of urticaria and angioedema are often easily identified, there are instances in which other cutaneous disorders may mimic these eruptions (Tables XXI, XXII). For example, the annular and arcuate morphology of some urticarial lesions must be differentiated from a group of disorders termed the figurative erythemas. This group includes erythema annulare centrifugum, erythema chronicum migrans and erythema marginatum. In contrast to urticaria, these eruptions usually are non pruritic. Erythema annular centrifugum, which most closely resembles an urticarial reaction pattern, can be identified by a characteristic scaling ring that trails its advancing red border. Individual lesions of erythema multiforme also may appear urticarial in their morphology; however, these usually are accompanied by more typical target-like lesions in the same patient. Early in their course, some primary blistering disorders may assume an urticarial morphology. In particular, the immune-mediated blistering disease, dermatitis herpetiformis, can initially appear as pruritic grouped individual papules. More typically, this disorder is manifested by grouped vesicles and can be readily differentiated from urticaria by a cutaneous biopsy. Similarly, herpes simplex and herpes zoster may initially present as pruritic, slightly painful urticarial lesions, and in some instances, the full clinical expression of grouped vesicles may not occur. Lesion arrangement (grouped) and a focal anatomical distribution, however, provide important clinical characteristics for differentiating herpetic lesions from urticarial reaction patterns. Similarly, we have observed patients with bullous pemphigoid who initially presented with urticaria-like lesions. Once again, a cutaneous biopsy differentiates this disorder from an urticarial reaction. Patients with mastocytosis frequently develop urticarial wheals at the sites of focal cutaneous mast cell infiltrates. However, close examination of the patient usually reveals the typical macular, papular or nodular lesions of mastocytosis. There are several disorders that also may mimic lesions of angioedema. These include panniculitis, cellulitis, thrombophlebitis, lymphangitis, and cheilitis granulomatosa (Table XXII).

Table XXI

Differential Diagnosis of Urticaria

Erythema Annulare Centrifugum
Erythema Marginatum
Erythema Chronicum Migrans
Erythema Multiforme
Dermatitis Herpetiformis
Bullous Pemphigoid
Herpes Simplex/Zoster
Mastocytosis

Table XXII

Differential Diagnosis of Angioedema

Panniculitis
Cellulitis
Thrombophlebitis
Lymphangitis
Cheilitis Granulomatosa

Once the clinical diagnosis of urticaria/angioedema has been established, careful attention to both the morphology and the anatomical distribution of these lesions may provide insight into potential etiologic factors. Small 1 to 3 mm wheals with large surrounding areas of erythema suggest the diagnosis of cholinergic urticaria. Focal, urticarial lesions with geometric shapes (linear, angular, straight-edged, etc) indicate the presence of external influences as may be seen in cold and pressure-induced urticarias. Similarly, lesions localized to exposed areas suggest the possibility of a solar or cold-induced urticarial reaction. In patients with only distal extremity involvement, the diagnosis of papular urticaria or urticarial vasculitis should be considered, while small urticarial papules with a follicular-like arrangement suggest the possibility of aquagenic urticaria.

The extent of diagnostic testing in patients with chronic urticaria/angioedema should be based on the interpretation of information gained from the history and physical examination. For example, if the diagnosis of urticarial vasculitis is suggested, then a skin biopsy should be performed along with obtaining complement levels, ANA, urinalysis and pulmonary function tests. If HAE is a diagnostic consideration, then C_1 INH, C_1, C_4 and C_2 levels should be obtained. Patients suspected of having cholinergic urticaria can be exercised in an attempt to induce their cutaneous lesions. In cases of urticaria/angioedema where the history and physical exam fail to uncover a potential etiologic factor(s), it has been recommended that the work-up be supplemented with a complete blood count, including a differential, an erythrocyte sedimentation rate, urinalysis, SMA 12 and sinus and dental x-rays. Except for x-rays, it recently has been argued that these other tests rarely uncover additional etiologic factors (Jacobson et al., 1980).

TREATMENT

The most effective approach to the treatment of urticaria/angioedema is the identification and elimination of the causative agent(s). In patients with medication or food-induced eruptions for example, avoidance of these substances is curative. In cases of physical urticarias, an explanation of the disease process and its initiating factors permits the patient to modify his/her particular lifestyle. For example, patients with cold urticaria should be warned of the potential danger of swimming in cool water and should never swim alone. Common sense measures such as wearing warm socks and gloves and protecting one's face from the cold air can markedly reduce the frequency of symptomatic episodes. Those patients with solar urticaria should be instructed on the use of combined UVB and UVA sunscreens and avoid direct sun exposure. In addition, the gradual increase in natural or artificial light exposure may effectively induce tachyphylaxis to light-induced urticaria. The use of chloroquine also may be effective in controlling some solar urticaria patients. In cases of papular urticaria secondary to insect bites, the use of insect repellants and treatment of household pets often are effective measures. Obviously patients who have underlying infections or other systemic disorders should have their treatment directed specifically at these diseases.

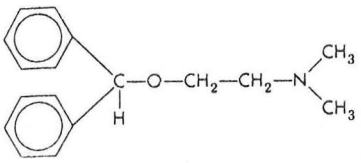
Unfortunately, in approximately fifty to seventy-five percent of the patients with chronic urticaria/angioedema, no etiologic factor(s) can be identified. Nevertheless, because of the morbidity (pruritus, cosmetic effects) associated with these skin eruptions some form of therapy is usually necessary. In the following sections, a rational, although empirical, approach to the treatment of chronic urticaria/angioedema is presented.

Avoidance of Salicylates and NSAIA: Because 40% to 50% of patients with chronic urticaria and angioedema may experience an exacerbation of their clinical disease with salicylate ingestion, avoidance of aspirin and NSAIA is recommended. In cases where aspirin sensitivity is evident, patients should also avoid exposure to azo dyes and benzoates.

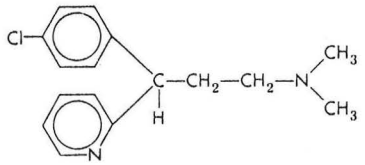
Antihistamines: Because the cutaneous mast cell and its released mediators play a central role in urticarial reactions, therapy directed at blocking the effects of the mast cell mediator histamine is warranted. Indeed, H_1 receptor antagonists have proven to be effective in controlling many but not all patients with urticaria. Six major pharmacologic groups with H_1 antagonist activity are now recognized (Tables XXIII, XXIV). Like histamine, most H_1 antagonists contain a substituted ethylamine moiety; however, unlike histamine, these agents have a tertiary amino group linked by a two or three atom chain to two aromatic substitutes. Although most H_1 antihistamines have similar properties, individual patients may note a superior therapeutic response to one class or one particular agent. For example, cyproheptadine has been reported to be more effective than other H_1 antagonists in controlling patients with cholinergic urticaria. In some instances, two different H_1 antihistamines may prove to be superior to either alone. In this latter case, it is recommended that agents representing two different classes of H_1 antagonists be employed for maximal therapeutic benefit. A new type of H_1 antihistamine has emerged on the commercial market. These agents differ from previous preparations in their kinetics of binding and dissociation from the histamine receptor and by their lack of soporific and anticholinergic effects. Terfenadine and astemizole are two such agents already available and soon to be released in the USA, respectively. Studies to date indicate that terfenadine is as effective as other H_1 antagonists in controlling lesions of chronic urticaria, but has the added advantage of not inducing significant sedation (Ferguson et al., 1985). In a double-blind study examining the therapeutic efficacy of astemizole versus placebo in 51 chronic urticaria patients, 84% of the patients receiving active drug had an excellent to good response while 30% of the placebo-treated patients noted improvement. Only two of thirty-eight patients ultimately treated with astemizole experienced sedation (Bernstein and Bernstein, 1986). Further clinical trials will be necessary to establish the importance of these medications in the management of chronic urticaria.

Because histamine mediates its effects through both H_1 and H_2 receptors, the H_2 antagonists, cimetidine, also has been used in combination with H_1 blockers in the management of chronic urticaria patients. Although the efficacy of this combination therapy has been questioned (Commens and Greaves, 1978), the addition of an H_2 antagonist to an H_1 antihistamine is worthwhile in patients with urticaria who are unresponsive to H_1 treatment alone (Monroe et al., 1981).

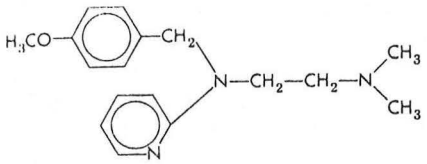
REPRESENTATIVE H_1-RECEPTOR BLOCKING DRUGS



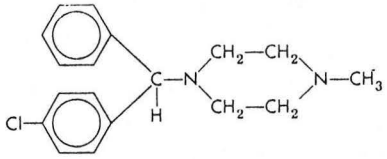
Diphenhydramine * (an ethanolamine)



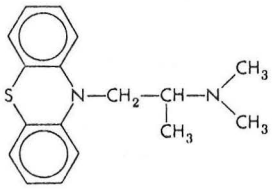
Chlorpheniramine † (an alkylamine)



Pyrilamine † (an ethylenediamine)



Chlorcyclizine § (a piperazine)



Promethazine (a phenothiazine)

* Dimenhydrinate is a combination of diphenhydramine and 8-chlorotheophylline in equal molecular proportions.
† Tripelennamine is the same less H_3CO. ‡ Pheniramine is the same less Cl. § Cyclizine is the same less Cl.

PREPARATIONS AND DOSAGE OF REPRESENTATIVE H_1-BLOCKING AGENTS *

CLASS AND NONPROPRIETARY NAME	TRADE NAME	DURATION OF ACTION (HOURS)	PREPARATIONS †	SINGLE DOSE (ADULT)
Ethanolamines				
Diphenhydramine hydrochloride	BENADRYL and others	4–6	O,L,I,T	25–50 mg
Dimenhydrinate	DRAMAMINE and others	4–6	O,L,I	50 mg
Carbinoxamine maleate	CLISTIN	3–4	O	4–8 mg
Ethylenediamines				
Tripelennamine hydrochloride	PBZ	4–6	O,T	25–50 mg; 100 mg (sustained release)
Tripelennamine citrate	PBZ		L	37.5–75 mg
Pyrilamine maleate		4–6	O	25–50 mg
Alkylamines				
Chlorpheniramine maleate	CHLOR-TRIMETON and others	4–6	O,L,I	4 mg 8–12 mg (sustained release) 5–20 mg (injection)
Brompheniramine maleate	DIMETANE and others	4–6	O,L,I	4 mg 8–12 mg (sustained release) 5–20 mg (injection)
Piperazines				
Hydroxyzine hydrochloride	ATARAX and others	6–24	O,L,I	25 mg
Hydroxyzine pamoate	VISTARIL	6–24	O,L	25 mg
Cyclizine hydrochloride	MAREZINE	4–6	O	50 mg
Cyclizine lactate	MAREZINE	4–6	I	50 mg
Meclizine hydrochloride	ANTIVERT and others	12–24	O	25–50 mg
Phenothiazines				
Promethazine hydrochloride	PHENERGAN and others	4–6	O,L,I,S	25 mg

* For a discussion of phenothiazines, *see* Chapter 19.
† Preparations are designated as follows: O = oral solids; L = oral liquids; I = injection; S = suppository; T = topical. Many H_1-blocking agents are also available in preparations that contain multiple drugs.

Tricyclic Antidepressants: An alternative to conventional H_1 antihistamine therapy is the use of tricyclic antidepressant agents which are known to be potent antagonists at the H_1 receptor. Doxepin, a heterocyclic variant of amitroptyline, has been demonstrated *in vitro* to be nearly 800-fold more potent as an H_1 antagonist than diphenhydramine on a molar basis (Richelson, 1979). Sullivan (1982) has reported the *in vivo* efficacy of this agent by showing its ability to inhibit a histamine-induced wheal and flare reaction in normal subjects, and Harto et al. (1985) have proven its efficacy in the treatment of chronic urticaria. Recently doxepin also has been reported in a double-blind study to be superior to hydroxyzine and cyproheptadine in the treatment of cold-induced urticaria (Neittaanmaki et al., 1984). On several occasions, we have found doxepin to be effective in controlling patients with chronic urticaria who were otherwise unresponsive to other H_1 antihistamines.

Disodium cromoglycate and related agents: Oral disodium cromoglycate has proven effective in controlling the pruritus and whealing in patients with mastocytosis (Soter et al., 1979); however, its benefit (if any) for urticaria patients has not been substantiated. Doxantrazole, a cromoglycate-like agent which is better- absorbed orally, has been shown to reduce whealing in patients with cold-induced urticaria (Bentley-Phillips et al., 1978). Ketotifen is a benzocycloheptathiophene derivative with both mast cell-stabilizing qualities and H_1 receptor antagonist activity. This agent has proven effective in treating patients with physical urticaria, chronic idiopathic urticaria and mastocytosis (Huston et al., 1986; Saiban, 1981; Czarnetzki, 1983). Oxatomide is a diphenylmethyl piperazine derivative of a substituted benzimidazole and has pharmacologic activities similar to ketotifen. This agent also has proven effective in controlling chronic urticarial reactions in a double-blind study (Peremans et al., 1981). Although these latter three agents have undergone testing in Europe, they are not presently available in this country.

Systemic Corticosteroids: The use of systemic corticosteroids is sometimes indicated in patients experiencing an acute urticarial reaction, and may be effective in controlling severe exacerbations in patients with idiopathic chronic urticaria. They are, however, to be avoided on a long-term basis in the management of patients with chronic urticaria. An exception to this statement pertains to treatment of patients with urticarial vasculitis who may require daily or alternate day systemic therapy.

SUMMARY

Urticaria and angioedema represent cutaneous reaction patterns for which multiple etiologic factors have been identified. The pathogenesis of these skin eruptions centers on the activation of the tissue mast cell and the subsequent release of its vasoactive and chemoattractant mediators. Local release of neuropeptides, infiltrating leukocytes, and elaboration of their inflammatory molecules also appear to be important in the clinical expression of these disorders. Initial evaluation of patients with urticaria/angioedema reaction patterns should focus on performing a thorough history and physical examination. When the cutaneous diagnosis is in question, a skin biopsy should be performed. Additional diagnostic testing is dictated by the information gained from the

history and physical. Treatment of urticaria and angioedema should be directed at eliminating the etiologic agent(s) when possible. In instances where such factors cannot be identified or eliminated, empirical therapy should include: the avoidance of salicylates and the use of H_1 (and possibly H_2) antagonists. Initially, oral corticosteroids may be necessary to control patients' cutaneous and systemic symptoms. As our understanding of the forces responsible for the expression of urticaria/angioedema improve, more effective approaches to treatment should emerge.

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