

An Overview of Chronic Urticaria

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Abstract

Acknowledging urticaria as a symptom of mast cell degranulation is stressed. The biology of the mast cell, and the recognized immunologic and non-immunologic mast cell secretagogues are individually discussed, along with mechanisms of activation and mediators released. The major, pre-formed mediator histamine in the skin produces a prototypic, short-lived urticaria, however, the clinical spectrum and pattern of "hives" indicate that other mediators contribute to the polymorphism and variable behavior of this symptom.

The clinical assessment is almost exclusively restricted to the history and physical examination. Features to review and examine are presented. The cause of "acute" urticaria is identifiable (by history) in the majority of patients, and except for hives that accompany an anaphylactic reaction, these patients rarely present to the physician for care. The persistent, or "chronic" hiver whose history cannot elicit a cause, is rarely triggered by an individual trigger, despite extensive professional evaluation. Evidence to support changing the chronological, "acute" and "chronic" classification of urticaria to "identifiable" and "non-identifiable" triggered urticaria is discussed, as is the futility of extensive, costly laboratory work-ups.

The natural history of urticaria reveals that management should be directed toward allowing the patient to maintain an acceptable quality of life (with or without some urticaria), until the episode resolves.

Index Entries: Mast cells; serum; histamines; secretagogues.

Introduction

The classification of urticaria has been based arbitrarily, or by consensus, on the duration of the symptomatic episode. According to this traditional categorization, *chronic* urticaria are defined as lesions that

occur almost daily for at least 6 wk, and until 6 wk have passed, the urticaria are labeled *acute*. The appropriateness of this nomenclature has been rarely questioned, and it does not apply to those patients who experience repeated episodic bouts of urticaria, with symptom-free periods that are variably longer, shorter, or the same duration as the symptomatic periods. However, we must be aware that any attempt to define stages of an evolutionary or developmental continuum is innately doomed to criticism. However, arbitrarily delineated stages may provide a useful shorthand for discussion (1).

Reviews of urticaria (and angioedema) have appended a classification for urticaria based on etiology, and/or specific stimuli to the chronological taxonomy. This designation is useful as a guide on etiology and possible therapeutic strategies. Thus, the management of urticaria would be better directed to those with a single identifiable “trigger” or cause, and those with no single identifiable “trigger” or cause—regardless of chronology! This overview will discuss urticaria, not by their duration, but by pathophysiologic mechanisms, and specific triggers, if known.

Pathophysiology of Urticaria (2)

Urticaria is the clinical manifestation of a localized increase of permeability of capillaries and small venules in the dermal papilla. An injection of histamine (a vasoactive agent) into the skin will produce a prototypic hive. This “Triple Response of Lewis” demonstrates 1) *erythema*—the clinical expression of vasodilation; 2) *a wheal*—reflecting vascular leakage; and 3) *pruritus*—the result of activation of itch receptors in the epidermis. An additional significant feature of the “Triple Response” caused by histamine is its spontaneous dissipation within 1 h. From this we may assume that histamine is probably not the sole inflammatory mediator causing clinical urticaria that last more than 1 h. Thus, urticaria must be regarded as a symptom of mast cell and/or basophil activation and degranulation. For the management of clinical urticaria is essential to be cognizant of the function and behavior of mast cells, basophils, and other inflammatory cells and mediators and cytokines.

Mast Cells/Basophils

Mast cells (MC) are essential, multipotent effector cells of the immune system (3). They house an array of biologically active mediator substances in their metachromatic granules (4). MC also express a number of functionally important cell-surface receptors, including high-affinity IgER(FcεRI), stem-cell-factor receptor (SCFR=c-kit), complement receptors (C3a and C5a), neuropeptide receptors (sub-

stance P), integrins, and cytokinal receptors. Less physiologically important receptors found on the mast cell include: FcεRII and FcεRIII (that bind IgE), and eosinophilic major basic protein, each of which may activate or regulate mast-cell secretion. Activation by a threshold number of these receptors can immunologically induce or promote degranulation, migration, and cytokine production (5). Although mast cells and basophils have many similarities, each is distinctive. Mast cells are found in connective tissues, where they often lie adjacent to blood and lymphatic vessels, near or within nerves beneath epithelial surfaces that are exposed to the external environment, such as those of the respiratory and gastrointestinal tract (mucosal mast cells = MMC) and the skin (connective-tissue mast cells = CTMC). Basophils are present in the circulation, and participate in the late-phase allergic reaction. The special demands of their function require the noted variable "mast-cell heterogeneity," manifested as phenotypic dissimilarities in morphology, histochemistry, mediator content, and response to drugs and stimuli of activation (6).

Recent evidence suggests that MMCs and CTMCs are derived from the same precursor cell, with the end-cell phenotype depending on factors found in the local microenvironment (7,8). With specific immunologic and non-immunologic stimulation, mast cells and basophils release or elaborate a diverse array of potent pro-inflammatory mediators. Once the mast cell degranulates, it requires 2–3 wk for new granules to replenish (9). Because of their key role in our host defense system, perhaps they should be regarded as "master" cells, rather than their original misnomer "mast" (Ger.: to fatten) cell, believed to be a source of nourishment for the surrounding tissue.

Mast-cell and basophil activators (or secretagogues) have been classified as a) immunologic; and b) non-immunologic "triggers" (10). Thus, classifying urticaria according to the underlying mechanism of mast-cell degranulation would be helpful. (see Table 1) Immunologic triggers activate the innate and/or adaptive mechanisms of the body's host defenses. The non-immunologic secretagogues trigger a diverse mediator release through exploitation of physiologic-cell function. The diversity of clinical urticaria results from the many different triggers.

Some still debate whether the number of cutaneous mast cells in patients with persistent urticaria are increased (11,12) or unchanged (13). However, it has been generally agreed that they respond with a lowered threshold of releaseability (14).

Immunologic Activators

Immune responses are inflammatory reactions induced by leukocytes, as a response to their detection of a pathogen or other foreign agent by *specific receptors on their cell membrane*. Some of the specific

Table 1
Classification of Urticaria
(According to underlying mechanism)

Immunologic	
IgE (FceRI)-mediated:	
Drugs:	Penicillin, porcine insulin, dextran
Foods:	Nuts, shellfish, eggs, milk
Hymenoptera:	Bees, wasps, yellow jackets
Contactants:	Latex, pets
IgG autoantibodies to the IgE receptor:	
Inhalants:	Pollens, animal dander
Physical:	Dermographism, cold, solar
C3a, C5a immune-complex/ anaphylotoxin-mediated:	
Urticarial vasculitis:	Rheumatoid arthritis SLE, Sjogrens, Hepatitis B or C Infection, Serum sickness, drugs penicillins, cephalosporins, sulfas
Haptens:	SP, somatostatin, VIP, gastrin
Neuropeptides:	IL-1, IL-3, RANTES,
Cytokines (HRFs):	
c-KIT (SCGF):	
Non-immunologic	
Direct mast-cell activators:	
Opiates, RCM, dextran, polymyxin, peptides (in jellyfish, lobsters, strawberries)	
Arachidonic acid metabolism:	
Aspirin, NSAIDs	
Kinin metabolism:	
ACE inhibitors	
Miscellaneous:	
Physical: heat, delayed pressure, aquagenic, vibratory	
?Thyroid autoimmunity	
Mechanism Unknown	
Idiopathic	
Drugs	
Vancomycin, ciprofloxacin, rifampin, thiopental, thiamine, amphetamine, alcohol, papaverine, tolazoline	

receptors present on all mast cells include: 1) the high-affinity FcεRI receptor (15); 2) C3a and C5a receptors; 3) neuropeptide receptors; 4) cytokine receptors; and 5) the stem-cell factor (also known as mast-cell growth factor) receptor, the KIT protein.

FcεRI Receptors

“Immediate-type” immunologic activation of mast cells and basophils is initiated by the crosslinkage of IgE antibody binding to FcεRI receptors. The prerequisite for immediate-type reactions precludes a patient’s genetic predisposition to produce specific IgE antibodies to that antigen (a macro-molecular protein, or a hapten found in drugs, foods, and latex), which then must sensitize the mast cells, and basophils (16).

When crosslinking of two adjacent high-affinity *IgE receptors* on the surface of the mast cell by its specific IgE antigen (or by lectins, or IgG anti-IgE-receptor antibody) occurs, the mast cell is activated to release its preformed pro-inflammatory mediators within minutes. When a threshold number of receptors are “bridged” (1% or fewer of its receptors) (17), the mast-cell membrane becomes activated (via the cyclo-oxygenase/arachidonic acid metabolic pathway), and there is an influx of Ca⁺ ions from the intercellular space (18). (Both basophils and non-IgE mast-cell secretagogues may not require calcium for activation) (19). A concomitant generation of intracellular cAMP (20) and the presence of Ca⁺ initiate movement of the mast-cell granules toward the cell surface, where they fuse with the cell membrane and release their (preformed) contents into the extracellular space (21).

IgE receptors can be activated by secretagogues other than IgE antigens, such as “auto-antibodies,” and lectins (i.e., PHA, ConA, and strawberries) (22,23).

This IgE-dependent activity raises the question, “Are atopics who have a genetic predisposition to produce increased amounts of IgE more susceptible to IgE-induced urticaria?” The literature does not support an increased incidence of chronic urticaria among atopics. Drugs are considered the most common allergic cause of urticaria, followed by foods, and then by latex. Urticaria caused by inhaled allergens is almost always associated with upper- and lower-airway symptoms and usually is transient (e.g., caused by an exposure to cats or horses). More prolonged seasonal urticaria associated with hay fever has been reported, but is very rare (24)

C3a and C5a Receptors

Complement is part of the innate immune system, and underlies one of the main effector mechanisms of antibody-mediated immunity. One of its physiologic activities is the disposal of immune complexes

and other products of inflammatory injury (25). If immune complexes, released by chronic infection or “auto-immune” diseases, the C3a and C5a receptors present on mast cells, neutrophils, eosinophils, and basophils can be activated and release their respective pro-inflammatory mediators (26).

In *serum sickness*, circulating immune complexes activate the complement cascade, resulting in a decrease in total hemolytic complement and the production of C3a and C5a. Since serum sickness reactions occur only with antigen excess, as more antibody is formed and the reaction moves into antibody excess, the reaction resolves spontaneously (27). The associated urticaria appear a few days to 3 wk after exposure to the inciting agent. The clinical spectrum of serum sickness includes fever, pruritus, urticaria, and angioedema, painful joint swelling, fatigue, lymphadenopathy, and occasionally nephritis—all accompanied by eosinophilia. These reactions are frequently seen after the injection of heterologous serum, penicillin, streptomycin, sulfonamides, and globulin preparations (28).

Viral infections are the most common cause of episodic urticaria in childhood (29). Urticaria occurs in 30% of patients with serum hepatitis during the preicteric phase, but urticaria is also seen in hepatitis A (30), B, and C (31) infections and other viral infections: herpes, varicella-zoster, rubella, measles, mumps, Epstein-Barr, cytomegalovirus (CMV), influenza, adenovirus, and enterovirus (32–34). Those rare cases of urticaria induced by parasitic infestation is not complement dependent.

Hereditary and acquired angioedema are not accompanied by urticaria (35).

Neuropeptide Receptors

Neuropeptides are the neurotransmitters, which interconnect the nervous system with the immune system. Neuropeptides, such as substance (SP), are also endogenous to the immune system, and function in the bidirectional communication between the immune and neuroendocrine systems, such as Substance P (SP) (36,37). Sensory nerves function as an afferent system to conduct stimuli from the skin to the CNS, and also act in an efferent “neurosecretory” role. Antidromic stimulation of the sensory nerves releases SP, calcitonin gene-related peptide (CGRP), and vasoactive intestinal protein (VIP), which promptly binds to its specific mast-cell receptor resulting in erythema, with or without a wheal (38–40).

An increased sensitivity of the microvasculature to VIP has been reported in patients with chronic idiopathic urticaria (CIU) (41). SP can act either on the mast-cell receptors or directly on blood vessels, but its release explains the exacerbations noted with local minor trauma (i.e.,

pressure urticaria), and “stress-induced” urticaria (42,43). Neuropeptides also contribute to the evolution of physical urticaria (44). Capsaicin depletes SP in the nerve endings when applied repeatedly to the skin, and inhibits the development of aquagenic urticaria (45) and cold- and heat-induced urticaria (46). In addition, chronic urticaria exacerbations caused by anxiety is mediated by release of neuropeptides, resulting in increased blood flow to the upper cutis, and increased skin temperature (47).

Histamine-Releasing Factors

Histamine-releasing factors (HRF) comprise a heterogeneous group of cytokines, released from stimulated mononuclear cells (48) that are capable of mediating histamine release from basophils and mast cells. Several groups of molecules with histamine-releasing activity have been discovered, including interleukins, chemokines, and an IgE-independent HRF (49). HRF is believed to be the factor responsible for the persistent urticaria in those chronic urticaria patients who do not demonstrate anti-IgE receptor antibodies. Cytokines reported to activate or prime basophils for histamine release include: IL-1, IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), connective tissue activating peptide III, macrophage inflammatory protein 1a and 1b, neutrophil-activating peptide-2, monocyte chemotactic and activating factor, and regulated on activation, normal T-cell-expressed and secreted chemotactic factor (RANTES) (50). The exact role that HRFs contribute to the clinical disease in chronic urticaria and/or angioedema has not been fully established.

KIT, the Receptor for Stem-Cell Factor (Mast-Cell Growth Factor)

It has been recently noted that activation of this mast-cell-surface receptor directly stimulates MC secretion and potentiates IgE-receptor-mediated MC degranulation and cytokine production (51,52). This receptor is considered a potent activator of mast cells, capable of triggering mast-cell degranulation alone or in synergy with other immunologic or non-immunologic stimuli (53).

Non-immunologic Secretagogues

These agents cause degranulation of mast cells and/or basophils through mechanisms that do not involve cell-surface receptors. The identifiable mechanisms of non-immunologic secretagogues are:

1. Direct effect on the mast cell or basophil;
2. Modulation of the mast-cell responsiveness;
 - a) via the arachidonic acid/cyclo-oxygenase metabolic pathway, or
 - b) ionophorically

Direct Effect on Involved Cells

PHYSICAL STIMULI (54)

Specific physical stimuli, such as pressure, temperature changes, ultraviolet light, vibration, and contact with water are recognized “triggers” for mast-cell degranulation. The connection between the physical stimulus and the release of mediators from mast cells is poorly understood. Reactivity to a physical stimulus has been passively transferred (serum from the patient transfers the ability of the recipient’s skin to urticate when challenged with the physical stimulus) for dermatographism, cold urticaria, and two types of solar urticaria (55,56). Notably, the association of food and exercise in food-dependent exercise-induced anaphylaxis) following the ingestion of a food, both IgE and non-IgE mediated mechanisms have been implicated (57) (celery, crustaceans, and other foods are associated with IgE, and in other cases any food consumed prior to exercise is contributory). Other factors reported to interact with exertion-induced anaphylaxis include drug intake (58), menstrual cycle (59), and weather conditions (60).

Dermatographism occurs in 4–5% of healthy individuals. It is considered to be—and resembles—an exaggerated triple response of Lewis. When it is accompanied by (moderate) pruritus, it is called symptomatic dermatographism (61). Peak prevalence is in young adults. Dermatographia is not associated with atopy, but dermatographia may follow a cutaneous allergic reaction or become associated with various pathologic and physiologic conditions (62). Dermatographia may be associated with chronic urticaria.

(*Delayed*)-pressure urticaria (DPU) develops 4–6 h after pressure or trauma to the skin (63). Chronic urticaria patients may have associated delayed-pressure urticaria at sites of predilection, such as the hands and feet. DPU is not pruritic, and responds poorly to antihistamines.

Cold-induced urticaria is idiopathic in over 90% of cases. Hives develop 5–30 min after exposure to cold, and may be precipitated by wind, cold bathing, handling cold objects, and drinking cold foods or drinks. The relative drop in cutaneous temperature rather than the absolute low temperature is the critical factor. For example, an overheated subject who plunges into a cool swimming pool on a hot day can develop generalized *cold-induced urticaria*. The mast-cell degranulation may develop during the period of cold exposure, but more often develops during rewarming and persists for about 30 min before resolving spontaneously. Rare forms of cold urticaria include *delayed cold urticaria* and the inherited, autosomal dominant *familial cold urticaria*.

Secondary cold urticaria accounts for about 5% of patients with cold urticaria, and occurs in association with cryoglobulinemia, cryofibrinogenemia,

Table 2
Classification of Solar Urticaria (149)

Type	Spectrum	Mechanism
I	280–320 u	passive transfer
II	320–400 u	Unknown
III	400–500 u	Unknown
IV	400–500 u	passive transfer
V	280–500 u	Unknown
VI	400 u	Protoporphyrin IX photosensitivity

and cold hemolysins, often secondary to viral infections such as syphilis or hepatitis C, or autoimmune disorders associated with cryoglobulinemia.

Heat-induced (or cholinergic) urticaria results from the activation of cholinergic sympathetic autonomic-nerve fibers supplying eccrine sweat glands, after a period of exercise or a hot bath, or from a high fever. Cholinergic urticaria can be duplicated by intradermal injections of acetylcholine. In these cases, local anesthetics or topical applications of atropine inhibit the formation of the urticaria. The urticarial lesions are characterized by the small 2–5 mm wheal, surrounded by an erythematous flare, and lasting 20–60 min. The condition often remits spontaneously within several years.

Solar urticaria (64) is a rare idiopathic photodermatosis, in which erythema followed by a pruritic wheal is noted within 5 min of exposure to a specific wavelength of light, usually in the visible light range (65), and disappears rapidly (66). The severity of the reaction depends on the length of time of the exposure and the intensity of the solar irradiation (67). Six types of solar urticaria have been described (see Table 2). The diagnosis is established by the history and physical exam, and typed by photopatch testing to several wavelengths the light spectrum. A negative phototest result from a single source does not exclude a diagnosis of solar urticaria. A provocative test with natural sunlight may be required.

Aquagenic urticaria are rare, and the hives appear from 2–30 min after immersion in water (68), regardless of its temperature or source (tap or lake water). These pruritic, follicular, cholinergic-like wheals can be reproduced by applying wet compresses to the patient’s back for at least 30 min. Sensitized mast cells may be activated by a water-soluble antigens that diffuse through the epidermis (69,70).

Vibratory urticaria are rare, and can be induced by vigorous vibration applied to the skin by a lawn mower or jackhammer (71).

RADIOCONTRAST MEDIA

The activation of mast cells and basophils plays a role in the pathogenesis of anaphylactoid reactions that occur during the administration of iodinated radiocontrast media (RCM). The pathogenesis of radiocontrast media adverse effects cannot be explained by a single theory (72). Although hyper-osmolality may be an important factor in the activation of basophils, it is less relevant for mast cells. RCM induces only the release of preformed mediators (73). The direct release of histamine from mast cells and basophils, as well as an activation of the complement system by RCM, has been documented by Rice et al. (74). Iodine and shellfish allergy are not risk factors for RCM reactions.

OPIATES

Opiates stimulate opioid receptors on cutaneous mast cells to release histamine and other mediators in adequate amounts to cause pruritus, urticaria, tachycardia, and hypotension on a dose-dependent basis. Skin biopsies after morphine injections reveal mast-cell degranulation (75). Other mast cells do not degranulate when exposed to opioids (76). Endogenous opioids injected into the skin are minimally pruritogenic, but they can potentiate histamine-induced itch. Interestingly, opiates do not release histamine from basophils (77).

PEPTIDES

Peptides, which are found in the sting of jellyfish and the Portuguese man-of-war will produce a linear "contact" papular urticaria in most individuals (78). Although most of these reactions are not IgE-induced, there have been reports of positive RAST test results to some toxins in the venom of these coelenterates (79).

Peptides, unrelated to the lobster allergens, which leach out of the shell of a lobster, can cause contact urticaria. Similar non-IgE induced contact urticaria has been attributed to caterpillars, the weed nettles, and corals (80).

Modulation of the Arachidonic-Acid Metabolic Pathway

Modulation of the arachidonic-acid metabolic pathway by nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with acute urticaria/angioedema in sensitive individuals. The production of excessive cysteinyl-leukotrienes (Cys-LTs) LTC₄, LTD₄ and LTE₄ in susceptible individuals is the explanation, and NSAIDs may not activate the mast cell directly (81). ASA sensitivity has been reported to occur in 25–55% of patients with chronic urticaria (82). In this group of NSAIDs-sensitive patients, chronic urticaria precedes the development of NSAID sensitivity, and when the chronic urticaria resolves, the patient no longer reacts to NSAIDs (83). There are rare reports of IgE antibodies to ASA (84) and NSAIDs (85). Selective cyclooxygenase-2 (COX-2) inhibitors

may be a valid alternative for patients with adverse reactions to ASA or NSAIDs (86). Interestingly, there are no reports of patients with both urticaria and asthma (as in the Aspirin Triad patient) (87). This may be an example of the heterogeneity of the mast cells because each tissue-associated mast cell has a unique set of activators.

IONOPHORES

Notably, mast cells are activated by calcium ionophores, which cause calcium influx into the cell—a critical event in mast-cell perturbation. There are several calcium ionophore compounds, including RP-HPLC and A23187, utilized in the study of mast cells in vitro. The clinical significance of this type of secretagogue is unknown, but there are two reports in which calcium-channel blockers were successful in the treatment of chronic urticaria patients (88,89).

Mechanism Unknown

DRUG REACTIONS

Alcohol, amphetamines, ciprofloxacin, papavorine, rifampin, thiamine, thiopental, tolazoline, and vancomycin have each been reported to cause MC degranulation and/or urticaria. These drug-induced urticaria do not fulfill the criteria of an immunologic reaction; therefore, direct mast-cell activation is suspected.

MASTOCYTOSIS

This encompasses a wide spectrum of clinical conditions, characterized by a localized or a diffuse increased number of mast cells in the skin (urticaria pigmentosa) and/or internal organs (systemic mastocytosis). The clinical course in most cases and the presence of benign hyperplasia of mast cells implicates an abnormal stimulus, rather than a neoplastic process (90,91), although mast-cell leukemia may develop in rare cases. An increased local concentration of stem-cell growth factor (c-KIT ligand) has been identified in lesions of mastocytosis (92,93).

The diagnosis of mastocytosis can often be made by the clinical history and the visible cutaneous lesions. Dermatographia can be elicited (Darier's sign) in more than 90% of patients with mastocytosis (94).

IDIOPATHIC URTICARIA

Defined as "arising spontaneously or from an obscure or unknown cause," idiopathic urticaria can be diagnosed only after a complete clinical assessment has failed to identify a single "trigger" as the cause of the urticaria. Aside from the physical urticarias, the cause for persistent or episodic urticaria is rarely identified in our present state of knowledge; thus, the labels "idiopathic," persistent, or episodic are justified.

Urticaria remains a common disorder that affects as many as 25% of all people at some time during their lives (95–97). Although the precise incidence for patients seen by clinicians with "idiopathic" urticaria

will never be known, it is well-accepted that they make up more than 90% of all patients with hives. Patients labeled as idiopathic usually also have exacerbations with identifiable triggers, such as associated DPU or dermatographism, and exacerbations from NSAIDS, or febrile illnesses. These findings have led me to theorize that chronic urticaria represents a “twitchy mast-cell syndrome.”

Clinical Assessment: History and Physical Examination

The diagnosis of *persistent* and *episodic idiopathic urticaria* is made almost exclusively from an appropriate, complete history. This implies a comprehensive understanding of all the previously mentioned features of mast-cell/basophil activation. Significant factors for the assessment of data include:

1. Personal or family history of “atopy”
2. Drugs and foreign sera
3. Foods and additives
4. Physical stimuli
5. Occupational and hobby-related exposures
6. Complete past medical history and review of systems
 - a) Connective-tissue disease
 - b) Infection
 - c) Psychic factors
 - d) Neoplasms
 - e) Genetic
 - f) Previous treatments for urticaria
7. Physical examination
8. Diagnostic procedures (including skin biopsy), if indicated, or if available

Atopy is the familial and personal tendency to develop asthma, allergic rhinitis, and/or atopic dermatitis. It imparts a polygenic spectrum of immunologic aberrations, which includes:

- a) Th1/Th2-cell (transient) reversal—and their associated cytokine profiles (98)
- b) A propensity for increased IgE response to common antigens (99)
- c) High-affinity IgE receptors on Langerhans cells, mast cells, eosinophils, and Th2 cells (101–102)
- d) Hyper-releaseable mast cells and basophils (103)
- e) Eosinophilia (104)
- f) Atypical vascular lability in atopic dermatitis (105–107) (including white dermatographism).

Drugs and Foreign Sera

Drugs and foreign sera are the most common identifiable triggers of acute urticaria. A complete drug history must include all agents that have been ingested, injected, applied, inserted, instilled, and inhaled, including non-prescription medications, (colored) vitamins and tonics, herbals, and “alternative” medications.

IgE-induced reactions require prior sensitization to the antigen (i.e., beta-lactam antibiotics). They occur seconds to minutes after ingestion, are not dose-related, and may herald an anaphylactic episode. Most immune drug reactions are clinically evident within two weeks of the onset of therapy with the drug (108). Non-IgE reactions (i.e., opioids, NSAIDs, and vancomycin), occur upon first exposure, usually within hours to days after ingestion. These reactions are dose-related and may herald an anaphylactoid episode.

Foods and Additives

The prevalence of food-induced urticaria in the general population is unknown, although most patients and physicians believe that foods are the cause of most cases of chronic urticaria, at least initially (109). A review of the literature clearly suggests that foods are more often a trigger for short-lived, episodic urticaria rather than persistent urticaria (110).

Foods that provoke urticaria are almost always identified by the patient, after several episodes occurring within 2 hours of ingesting the putative food. Although urticaria may be the sole manifestation of an adverse reaction to a food, reactions in other sites such as the intestine, and/or respiratory system frequently accompany or precede the urticaria (111). Foods commonly implicated (in more than 85% of patients) as the cause of hives in sensitive subjects include egg, peanuts, milk, nuts, soy, wheat, fish, crustaceans, and shellfish. However, virtually any protein-containing food may be allergenic. Studies of the natural history of allergic reactions to foods in children suggest that many who experience urticaria following exposure to certain foods such as milk, egg, soy, or wheat early in life may later tolerate these foods without difficulty. Loss of sensitivity to other foods such as peanuts, tree nuts, or crustaceans (shrimp) occurs less frequently (112).

Routine skin or in vitro testing for foods is not recommended for patients with persistent urticaria. However, the negative predictive accuracy of properly performed tests is excellent, and the positive predictive accuracy of food skin tests is less reliable. Provocation testing is needed to confirm an allergic sensitivity (113).

Physical Stimuli

Physical stimuli usually produce hives within minutes of exposure and conform to the area exposed to the stimulus, allowing most affected

individuals to recognize the association. It is only when the onset of the reaction is atypical or significantly delayed (i.e., DPU) that the association may not be recognized. The clinical impression, obtained from the history, is readily confirmed by a provocative challenge with the physical stimulus. All patients should be tested for dermatographism, since patients who respond positively may benefit from the administration of H1 plus H2 antagonists (114,115). Testing for dermatographism is more likely to elicit a positive response on the back than on the forearm.

Occupational and Hobby-Related Exposures

Both immunologic and non-immunologic secretagogues have been noted to produce contact urticaria. The most complete list of those agents has been reported by Burdick and Mathias (117). Since contact urticaria includes a transient wheal-and-flare response at the site of cutaneous contact with the putative agent, the pattern of each episode should suggest an association with occupational or recreational exposure. Although 15% of patients with contact urticaria to latex also had a history of extracutaneous symptoms (i.e., respiratory and/or gastrointestinal), anaphylactic reactions are rare (116).

Complete Review of Systems

Urticaria is rarely, if ever, the sole symptom of an underlying disease. A complete review of systems is recommended, because other medical symptoms will reveal typical symptoms of those diseases in which urticaria has been described prior to or concomitant with the appearance of the urticaria.

Connective-Tissue Disease

Suspicion of a possible underlying connective tissue disease (e.g., systemic lupus erythematosus, hypocomplementemia urticarial vasculitis syndrome, serum sickness) is aroused by the appearance of urticarial lesions that persist for 24–48 h, which usually appear on the lower extremities and buttocks, and tend to hurt and burn more than itch. These urticaria usually blanch on diascopy, and leave residual ecchymosis at the sites of lesions. Associated rheumatic and systemic symptoms usually occur, as well as an elevated erythrocyte sedimentation rate (117).

Infection

As mentioned previously, several viral infections have been reported to be associated with urticaria, and hives related to infections are usually fleeting. More persistent urticaria (lasting 3–4 wk) have been reported to occur with a variety of parasitic infestations, including

ascaris, amoebae, giardiasis, hookworm, strongyloidiasis, shistosomes, echinococcus, filariasis, malaria, and fascioliasis (84). However, since routine testing of stool specimens for ova and parasites is rarely helpful, special considerations should be given only to those patients who exhibit GI symptoms and demonstrate eosinophilia on the complete blood count.

Expensive and exhaustive searches for occult infections are presently considered unwarranted, because even when infection is found, treatment rarely affects the hives. Examples of infections that are associated with chronic urticaria but lack substantial support in the literature are chronic sinusitis, *Helicobacter pylori* infection of the duodenum, and chronic Trichophyton infection of the skin.

Psychic Factors

Most clinicians and patients associate exacerbations of "chronic" urticaria with emotional stress. No characteristic personality profile for patients with chronic urticaria has been identified (118–120). Chronic urticaria is not a psychosomatic illness, although patients' quality of life is greatly affected by chronic urticaria and by the side effects of the treatment. As noted above, "stress" releases neuropeptides, which can synergistically act on hyper-responsive mast cells.

Neoplasms

There have been reports of chronic urticaria associated with neoplasms, but this connection is exceedingly rare. The exception is acquired C1-inhibitor deficiency-induced angioedema. The acquired angioedema type II is associated with lymphoproliferative disorders such as multiple myeloma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia.

The *Schnitzler syndrome* is characterized by a chronic urticarial eruption with a monoclonal IgM gammaopathy. The other signs of the syndrome include intermittent fever, joint and/or bone pain, lymphadenopathy, elevated ESR, and leukocytosis. Fifteen percent of patients with the Schnitzler syndrome progress to lymphoplasmocytic malignancy (121).

Current available information does not warrant routine use of an exhaustive evaluation for an occult neoplasm for the urticaria/angioedema patient.

Genetic Factors

Familial cold urticaria, delayed cold-induced urticaria, familial localized heat, and solar urticaria associated with erythropoietic protoporphyria, aquagenic, and vibratory urticaria have all been described as genetic types of urticaria. Among the patients afflicted with familial urticaria that is not associated with physical agents, the syndrome of

urticaria, deafness and amyloidosis, Muckle-Wells syndrome should be considered (122).

Miscellaneous

Single case reports of urticaria that appears with unusual conditions should be regarded as oddities. Isolated reports have identified a patient with chronic urticaria and parathyroid disease (123), and chronic urticaria and polycythemia vera, Waldenstrom's macroglobulinemia, and cystic fibrosis (124).

Results of Treatment to Date

Most patients have already taken antihistamines (by prescription or over-the-counter) before seeking a consultation with a specialist. Antihistamines are not "prn" drugs for a chronic medical problem such as chronic urticaria, and the more H1-receptors that are occupied, the better the results for those patients who are antihistamine responders. Side effects are a limiting factor for many of the antihistamines. The non-sedative, second-generation antihistamines are more conducive to compliance, and allow for toleration of more than the manufacturer's recommended doses. A small number of patients may require the addition of systemic corticosteroids to attain "comfort."

Physical Examination

A complete physical examination is necessary to identify the possibility of any significant underlying pathology. Particularly germane physical findings would include the appearance of the skin (urticaria pigmentosa), joint abnormalities, organomegaly, lymphadenopathy, thyroid enlargement, and vital signs.

The appearance of the urticaria may provide a clue to etiology and possible management. A greater resemblance to the Triple response of Lewis indicates the presence of more histamine in the lesion. Antihistamine therapy is most effective when there is more histamine in the lesion. The less it resembles the Triple response of Lewis, the greater the probability that there are other mediators in the lesion, and the less responsive they will be to antihistamines alone. *Papular urticaria*—which are very pruritic, and persist longer than ordinary hives—on exposed parts of the body may indicate insect bites (i.e., fleas (125), bedbugs, scabies (126), and some other mites (127)). Linear wheals suggest *dermatographism*, and *delayed-pressure urticaria* (DPU) if they appear under belts or straps. Lesions limited to exposed areas are probably caused by *solar* or *cold* conditions. Purpuric lesions that appear mainly on the lower extremities suggest *urticarial vasculitis*.

Angioedema occurs with urticaria in one-half of the patients with persistent urticaria. It is always episodic (never persistent), and the

individual swelling always lasts longer than an individual hive and is almost always non-pruritic. Prognostically, when chronic urticaria occurs with episodic angioedema, the duration often persists for a longer period than those with urticaria alone.

Diagnostic Procedures

Careful history and physical examination and directed laboratory evaluation remain the cornerstone in the evaluation of this disorder. Only clues obtained from the history and physical examination should be pursued by diagnostic procedures. Routine laboratory tests have consistently proven most disappointing for the identification of an etiology (128–130).

Approximately 5–25% of patients with “chronic” urticaria have antithyroid autoantibodies, but these patients are clinically and biochemically euthyroid (131,132). Anti-peroxidase and anti-thyroglobulin autoantibodies should be assessed in all patients with refractory chronic urticaria (133). Although there is anecdotal evidence that treating these patients with exogenous thyroid hormone leads to a significant improvement of their urticaria (134–136).

A link between urticaria and skin diseases—particularly *Helicobacter pylori*—has been suggested. Reported results for an association with urticaria vary from convincingly positive (137,138) to definitive negative associations (139–141), and the most recent reports deny a causal relationship. Routine investigations for *Helicobacter pylori* are not recommended.

Reports have linked chronic urticaria and chronic hepatitis C, particularly when associated with cryoglobulinemia. Again, the history and physical exam is the most revealing diagnostic tool for the clinician.

A *skin biopsy* is indicated in severe cases of chronic or persistent urticaria, particularly when urticaria vasculitis is considered. Interpretation by a dermatopathologist who is familiar with urticaria is essential. See Table 2 for histologic clues which can help confirm an etiology or suggest specific therapy (i.e., neutrophils respond to colchicines and dapsone).

The *urticarial phase of bullous pemphigoid* and *urticarial vasculitis* are two important entities that require the special expertise of a dermatopathologist. A neutrophilic perivascular infiltrate without infiltration of the dermal vessels is observed in some severe cases of persistent urticaria, and may respond to a trial of dapsone and/or colchicine (142).

Natural History of Urticaria

To date, there is no evidence that the natural history of urticaria, whether linked to an identifiable cause or idiopathic, is influenced by

Table 2
Continuum of Histologic Changes of Urticaria

	Common urticaria	Intermediate group	Urticarial vasculitis
Location of infiltrate	Perivascular	Perivascular +/- within vessel walls	Perivascular + within vessel walls
Infiltrate cell type	Lymphocytes, histiocytes Eosinophils	Lymphocytes, histiocytes Neutrophils, eosinophils	Neutrophils
Leucocytoclasia	-	+/-	+
Perivascular fibrinoid deposition	-	+/-	+
Endothelial swelling	-	+/-	+
Extravasation of RBCs	-	+/-	+

treatment. Even persistent urticaria will eventually resolve. It is common for patients with persistent urticaria to have exacerbations during a course of effective treatment. A review of authors who have reported a course for “chronic” (persistent) urticaria (143–148) can be summarized as:

- 50% will resolve (with or without treatment) within 6 mo of onset
- 20% will resolve (with or without treatment) within 36 mo of onset
- 20% will resolve (with or without treatment) within 60 mo of onset
- <2% will resolve (with or without treatment) within 25 yr
- 50+% will experience at least one recurrence of “chronic” urticaria after an apparent spontaneous resolution.

Management of these patients should be directed to maintaining an acceptable quality of life (with or without some urticaria) until the episode resolves.

Summary

There is no “cure” for chronic urticaria! It is essential to explain to the patient that their hives may be a long-term problem that can be controlled with medications, so that they do not keep searching for some hidden cause. Although histamine is considered the major element, other mediators, cytokines, and inflammatory cells participate in the reaction. Consider the following:

1. Urticaria is a symptom of mast-cell activation, along with the participation of other cells.
2. Histamine is one of the major pro-inflammatory, vasoactive mediators producing a Triple Response of Lewis-like hive. The body's major sources of histamine are mast cells and basophils. The best therapeutic response is achieved by blocking as many H1 receptors as possible.
3. Other pro-inflammatory mediators, released from activated mast cells, basophils, eosinophils, neutrophils, and lymphocytes, produce the urticarial lesions. Anti-inflammatory medications such as corticosteroids may be required to suppress this cutaneous reaction.
4. The evaluation of patients with persistent urticaria requires a complete history and physical examination. Routine diagnostic testing is not recommended, but appropriate testing may be warranted from clues in the history and physical examination.
5. The goal of management is symptom relief, since chronic urticaria/angioedema ("twitchy mast-cell" syndrome) will resolve spontaneously eventually (months to years).

References

1. Diamond, J. From egalitarianism to kleptocracy, in *Guns, Germs, and Steel*. W.W. Norton & Co., London, 1999, p. 267.
2. Bressler, R.B. (1995), *Immunol. Allergy Clinics* **15**,659–677.
3. Shelburne, C.P. and Ryan, J.J. (2001), *Immunol. Rev.* **179**,82–93.
4. Czarnetzki, B.M. (1987), *Semin. Dermatol.* **6**,272–285.
5. Valent, P., Scherthaner, G.H., Sperr, W.R., et al. (2001), *Immunol. Rev.* **179**,74–81.
6. Galli, S.J. (1993), *N. Engl. J. Med.* **328**,257–264.
7. Kitamura, Y. (1989), *Annu. Rev. Immunol.* **7**,59–76.
8. Roitt, I., Brostoff, J., and Male, D., Hypersensitivity—Type I, in *Immunology*, 5th ed., Roitt, I., Brostoff, J., and Male, D., eds., Mosby, London, 1998, p. 307.
9. Schwartz, L.B. and Huff, T.F. Mast cells, in *The Lung: Scientific Foundations*, Crystal, R.G. and West, J.B., eds., Raven Press, New York, 1991, pp. 601–605.
10. Galli, S. Allergy, in *Fundamental Immunology*, 4th ed. Paul, E.D., ed., Lippincott-Raven Publications, Philadelphia, 1999, pp. 1143–1148.
11. Natbony, S.F., Phillips, M.E., Elias, J.M., et al. (1983), *J. Allergy Clin. Immunol.* **71**,177–183.
12. Haas, N., Toppe, E., and Henz, B.M. (1998), *Arch. Dermatol.* **134**,41–46.
13. Bedard, P.M., Brunet, C., Pelletier, G., et al. (1986), *J. Allergy Clin. Immunol.* **78**,1121–1125.
14. Schwartz, L.B. and Huff, T.F. Mast cells, in *The Lung: Scientific Foundations*, Crystal, R.G. and West, J.B., eds., Raven Press, New York, 1991, pp. 601–615.
15. Schwartz, L. and Huff, T. Biology of mast cells and basophils...
16. Mohapatra, S.S. and Lockey, R.F. *Allergens*, in *Current Review of Allergic Diseases*, Kaliner, M.A., ed., Current Medicine, Inc., Philadelphia, 1999, p. 51.
17. Coleman, J.W. and Godfrey, R.C. (1981), *Immunology* **44**,859.

18. Austen, F. (1984), The heterogeneity of mast cell populations and products. *Hosp. Pract.* The McGraw-Hill Companies, **19**,139.
19. Nolte, H. *Immunol. Allergy Pract.* **1002:14**,255–263.
20. Peachell, T., MacGlashan, Jr., D.W., Lichtenstein, L.M, et al. (1988), *J. Immunol.* **140**,571–575.
21. Siraganian, R.P. Mast cells and basophils, in *Current Review of Allergic Diseases*, Kaliner, M.A., ed., Current Medicine, Inc., Philadelphia, 1999, pp. 11–23.
22. Fieboger, E., Maurer, D., Holub, H., et al. (1995), *J. Clin. Investig.* **96**,2602–2612.
23. Nimi, N., Francis, D.M., Kerman, F., et al. (1996), *J. Investig. Dermatol.* 1006.
24. Walbott, G.L. and Merkle, K. (1952), *Ann. Allergy* **10**,30–35.
25. Walport, M.J. (2001), *N. Engl. J. Med.* **344**:14,1058–1066.
26. Roitt, I., Brostoff, J., and Male, D. Complement, in *Immunology*, 5th ed., Roitt, I., Brostoff, J., and Male, D., eds., Mosby, London, 1998, pp. 55–58.
27. Roitt, I., Brostoff, J., and Male, D. Hypersensitivity—Type II, in *Immunology*, Roitt, I., Brostoff, J., Male, D., eds., Mosby, London, 1998, p. 332.
28. Bork, K. Urticaria and angioedema, in *Cutaneous Side Effects of Drugs*, W.B.Saunders Co., 1988, p. 87.
29. Leaute-Labreze, C., Mortureux, P., and Taieb, A. Urticaria, in *Textbook of Pediatric Dermatology*—Vol. 1, Harper, J., Oranje, A., and Prose, N., eds., Blackwell Science Ltd, Oxford, 2000, pp. 587–599.
30. Dollberg, S., Berkun, Y., and Gross-Kieselstein, E. (1991), *Pediatr. Infect. Dis. J.* **10**,702–703.
31. Reichel, M. and Mauro, T.M. (1990), *Lancet* **336**,822–823.
32. Twarog, F.J. (1983), *Pediatr. Clin. N. Am.* **30**,887–898.
33. Mahmood, T. and Janniger, C. (1993), *Cutis* **52**,78–80.
34. Harris, A., Twarog, F.J., and Geha, R.S. (1983), *Ann. Allergy* **51**,161–165.
35. Donaldson, V.H. and Evans, R.R. (1963), *Am. J. Med.* **36**,37–44.
36. Lotti, T., Hautmann, G., and Panconesi, E. (1995), *J. Am. Acad. Dermatol.*
37. Theoharides, T.C., Singh, L.K., Boucher, W., et al. (1998), *Endocrinology* **139**,403–413.
38. Foreman, J.C. and Piotrowski, W. (1984), *J. Allergy Clin. Immunol.* **74**,127–131.
39. Valencia, M. and Randazzo, L. (1992), *Allergol. Immunopathol. (Madr)* **20**,3–8.
40. Borici-Mazi, R., Kouridakis, S., and Kontou-Fili, K. (1999), *Allergy* **54**,46–56.
41. Smith, C.H., Atkinson, B., Morris, R.W., et al. (1992), *Lancet* **339**,91–93.
42. Panconesi, E. and Hauptmann, G. (1996), *Dermatologic Clinics* **14**,399–421.
43. Singh, L.K., Pang, X., Alexacos, N., et al. (1999), *Brain Behav. Immun.* **13**,225–239.
44. Lowman, M.A., Benyon, R.C., and Church, M.K. (1988), *Br. J. Pharmacol.* **95**,121–130.
45. Lotti, T., Teofoli, M.D., and Tsampau, D. (1994), *J. Am. Acad. Dermatol.* **30**,232–235.
46. Cappugi, P., Lotti, T., Tsampau, D., et al. (1989), *Skin Pharmacol.* **4**,230.
47. Graham, D.T. and Wolf, S. (1950), *JAMA* **143**,1396–1402.
48. Elias, J., Boss, E., and Kaplan, A.P. (1986), *J. Allergy Clin. Immunol.* **78**,914–918.
49. Bheekha-Escura, R., Chance, S.R., Langdon, J.M., et al. (1999), *J. Allergy Clin. Immunol.* **103**,937–943.
50. Kuna, P. and Kaplan, A.P. (1996), *All Asthma Proceedings* **17**,5–11.
51. Taylor, A.M., Galli, S.J., and Coleman, J.W. (1995), *Immunology* **86**,427–433.
52. Maurer, M., Echtenacher, B., Hultener, L., et al.
53. Costa, J.J., Demetri, G.D., Harrist, T.J., et al. (1996), *J. Exp. Med.* **183**,2681–2686.
54. Schocket, A.L. Physical urticarias, in *Clinical Management of Urticaria and Anaphylaxis*, Schocket, A.L., ed., Marcel Dekker, Inc., New York, 1993, pp. 69–98.
55. Wanderer, A.A., Maselli, R., Ellis, E.F., et al. (1971), *J. Allergy Clin. Immunol.* **48**,13–22.
56. Sams, Jr., W.M. (1970), *J. Allergy* **45**,295–301.

57. Caffarelli, C., Cataldi, R., Giordano, S., et al. (1997), *Allergy Asthma Proc.* **18**,245–248.
58. Sheffer, A.L. and Austen, K.F. (1984), *J. Allergy Clin. Immunol.* **73**,699–703.
59. Dohi, M., Suko, M., Sugiyama, H., et al. (1991), *J. Allergy Clin. Immunol.* **87**,34–40.
60. Caffarelli, C., Cavagni, G., Giordano, S., et al. (1996), *J. Allergy Clin. Immunol.* **98**,762–765.
61. Warin, R.P. and Champion, R.H. Physical urticaria, in *Urticaria*, Warin, R.P. and Champion, R.H., eds., W.B. Saunders Co., Philadelphia, 1974, pp. 120–160.
62. Wong, R.C., Fairley, J.A., and Ellis, C.N. (1984), *J. Am. Acad. Dermatol.* **11**,643–652.
63. Sibbald, R.B. (1984), *Dermatol. Clin.* **4**,57–69.
64. Harber, L.C. and Bickers, D.R. Solar urticaria, in *Photosensitivity Diseases* (Harber, L.C. and Bickers, D.R., eds.) B.C. Decker, Inc., Toronto, 1989, pp. 209–218.
65. Uetsu, N., Miyauchi-Hashimoto, H., Okamoto, H., et al. (2000), *Br. J. Dermatol.* **142**,32–39.
66. Juhlin, L. and Malmros-Enander, I. (1986), *Photodermatology* **3**,164–168.
67. Ryckaert, S. and Roelandts, R. (1988), *Arch. Dermatol.* **134**,71–74.
68. Sibbald, R.G., Kobza-Black, A., et al. (1981), *Br. J. Dermatol.* **105**,297–302.
69. Czarnetzki, B.M., Breetholt, K.H., and Traupe, H. (1986), *J. Am. Acad. Dermatol.* **15**(Pt 1),623–627.
70. Sibbald, R.G., Black, A.K., Eady, R.A., et al. (1981), *Br. J. Dermatol.* **105**,297–302.
71. Patterson, R., Mellies, C.J., Blankenship, M.L., et al. (1972), *J. Allergy Clin. Immunol.* **50**,174–182.
72. Westhoff-Bleck, M., Bleck, J.S., and Jost, S. (1991), *Drug Saf.* **6**,28–36.
73. Stellato, C., deCrescenzo, G., Patella, V., et al. (1996), *J. Allergy Clin. Immunol.* **97**,838–850.
74. Rice, M.C., Lieberman, P., Siegle, R.L., et al. (1983), *J. Allergy Clin. Immunol.* **72**,180–186.
75. Levy, J.H., Adelson, D., and Walker, B. (1991), *Agents Actions* **34**,302–308.
76. Barke, K.E. and Hough, L.B. (1993), *Life Sci.* **53**,1391–1399.
77. Withington, D.E., Patrick, J.A., and Reynolds, F. (1939), *Anaesthesia* **48**,26–29.
78. Fisher, A.A. Contact urticaria, in *Contact Dermatitis*, Fisher, A.A., ed., Lea & Febiger, Philadelphia, 1986, pp. 686–709.
79. Burnett, J.W. and Calton, G.J. (1981), *Cutis* **27**,50–52.
80. Burdick, A.E. and Mathias, C.G.T. (1985), *Dermatol. Clinics* **3**,71–84.
81. Szczeklik, A. and Stevenson, D.D. (1999), *J. Allergy Clin. Immunol.* **104**,5–13.
82. Grzelewska-Rzymowska, I., Szmidt, M., and Rozniecki, J. (1992), *J. Invest. Allergy Clin. Immunol.* **2**,39–42.
83. Manning, M.E., Stevenson, D.D., and Mathison, D.A. (1992), *Immunol. Allergy Clinics* **12**,611–631.
84. Blanca, M., Perez, E., Garcia, J.J., et al. (1989), *Ann. Allergy* **62**,295–298.
85. Stevenson, D.D. Personal communication.
86. Bavbek, S., Celik, G., Ediger, D., et al. (1999), *J. Asthma* **36**,657–663.
87. Anderson, J.A. Drug allergy, in *Current Review of Allergic Diseases*, Kaliner, M.A., ed., Current Medicine, Inc. Philadelphia, 1999, pp. 190–202.
88. Bressler, R.B., Sowell, K., and Huston, D.P. (1989), *J. Allergy Clin. Immunol.* **83**,756–763.
89. Liu, R.Y., Pan, L.N., Hwang, S.C., et al. (1990), *J. Dermatol. Treatment* **1**,187–189.
90. Metcalfe, D.D. (1991), *J. Investig. Dermatol.* **96**(S),1–4.
91. Longley, J., Duffy, T.P., and Kohn, S. (1995), *J. Am. Acad. Dermatol.* **32**,54–61.
92. Longley, B.J., Morganroth, G.S., Tyrell, S.T., et al. (1993), *N. Engl. J. Med.* **328**,1302–1307.
93. Funasaka, Y., Boulton, T., Cobb, M., et al. (1992), *Mol. Biol. Cell* **3**,197–202.

94. VanGysel, D. and Oranje, A.P. Mastocytosis, in *Textbook of Pediatric Dermatology*, Harper, Oranje, A.P., Prose, eds., Blackwell Science, Oxford, 2000, p. 607.
95. Mathers, K.P. (1983), *J. Allergy Clin. Immunol.* **72**,1–18.
96. Doutre, M. (1999), *Eur. J. Dermatol.* **9**,601–605.
97. Mathews, K.P. Chronic urticaria, in *Clinical Management of Urticaria and Anaphylaxis*, Schocket, A.L., ed., Marcel Dekker, Inc., New York, 1993, pp. 21–53.
98. Leung, D.Y.M. (1999), *J. Allergy Clin. Immunol.* **104(suppl)**,S99–S108.
99. Bos, J.D., Woeremga, E.A., Smitt, J.H.S., et al. (1992), *Arch. Dermatol.* **128**,1509–1512.
100. Galli, S.J. (1993), *N. Engl. J. Med.* **328**,257–265.
101. Tanaka, Y., Takenaka, M., Matsunaga, Y., et al. (1995), *Arch. Dermatol. Res.* **287**,712–717.
102. Wollenberg, A., Kraft, S., Hanau, D., et al. (1996), *J. Investig. Dermatol.* **106**,446–453.
103. Lebel, B., Venencie, P., Saurat, J., et al. (1980), *Dermato-Venereol.* **95(suppl)**,57–59.
104. Boguniewicz, M., Nicol, N.H., and Leung, D.Y.M. Atopic disease and the skin, in *Cutaneous Allergy*, Charlesworth, E.N., ed., Blackwell Science, Cambridge, 1996, pp. 209–231.
105. Whitfield, A. (1938), *Br. J. Dermatol.* **50**,71–76.
106. Ely, H. (1997), *Cutis* **59**,67–73.
107. Sulzberger, M.B. and Herrmann, F. Pathogenesis and characteristics of disturbances in the delivery of sweat, in *The Clinical Significance of Disturbances in the Delivery of Sweat*, Sulzberger, M.B. and Herrmann, F., eds., Charles C. Thomas, Springfield, 1954, pp. 113–115.
108. Sullivan, T.J. Diagnosis and management of drug allergy, in *Clinical Management of Urticaria and Anaphylaxis*, Schocket, A.L., ed., Marcel Dekker, Inc., New York, 1993, pp. 119–139.
109. Bock, S.A., Sampson, H.A., Atkins, F.M., et al. (1988), *J. Allergy Clin. Immunol.* **82**,986–997.
110. Atkins, F.M. The diagnosis of food-induced urticaria, in *Clinical Management of Urticaria and Anaphylaxis*, Schocket, A.L., ed., Marcel Dekker, Inc., New York, 1993, pp. 141–156.
111. Metcalfe, D.D. and Sampson, H.A., eds. (1990), *J. Allergy Clin. Immunol.* **86**,421–442.
112. Bock, S.A. (1982), *J. Allergy Clin. Immunol.* **69**,173–177.
113. Sampson, H.A. and Albergo, R. (1984), *J. Allergy Clin. Immunol.* **74**,26–33.
114. Mansfield, L.E., Smith, J.A., and Nelson, H.S. (1983), *Am. Allergy* **50**,264–270.
115. Bleehen, S.S., Thomas, S.E., Greaves, M.W., et al. (1982), *Br. J. Dermatol.* **117**,81–91.
116. Burdick, A.E. and Mathias, C.G.T. (1985), *Dermatol. Clinics* **3**,71–85.
117. Berg, R.E., Kantor, G.R., and Bergfeld, W.F. (1988), *Int. J. Dermatol.* **27**,468–472.
118. Panconesi, E. Stress and skin diseases, in *Psychosomatic Dermatology*, J.B. Lippincott, Philadelphia, 1984, pp. 94–179.
119. Graham, D.T. and Wolf, S. (1950), *JAMA* **143**,1396–1402.
120. Wittkower, E.D. (1953), *Psychosom. Med.* **15**,116–126.
121. Lipsker, D., Veran, Y., Grunenberger, B.T., et al. (2001), *Medicine* **80**,37–44.
122. Muckle, T.J. (1979), *Br. J. Dermatol.* **100**,87–92.
123. Harvey, R.P., Moore, P.B., Kolterman, O.G., et al. (1981), *J. Allergy Clin. Immunol.* **67**,50 (abstr).
124. Laufer, P. (1985), *Cutis* **36**,245–246.
125. Lansford, C.J. (1949), *Arch. Dermatol. Syphilol.* **60**,1184–1202.
126. Witkowski, J.A. and Parish, L.C. (1984), *Cutis* **33**:277–279.
127. Burns, D.A. (1987), *Clin. Exp. Dermatol.* **12**,200–201.
128. Quaranta, J.H., Rohr, A.S., Rachelefsky, G.S., et al. (1989), *Ann. Allergy* **62**,421–424.
129. Jacobson, K.W., et al. (1980), *JAMA* **243**,1644.
130. Nelson, H.S. (1984), *JAMA* **251**,1680.

131. Leznoff, A. and Sussman, G.L. (1989), *J. Allergy Clin. Immunol.* **84**,66–74.
132. Turktas, I.N., Gokcora, S., Demirsoy, N., et al. (1997), *Int. J. Dermatol.* **36**,187–190.
133. Finn Jr., A.F. Urticaria and angioedema, in *Current Review of Allergic Diseases*, Kaliner, M.A., ed., Blackwell Science, Inc., Philadelphia, 1999, pp. 145–156.
134. Rumblyrt, J.S., Katz, J.L., and Schocket, A.L. (1995), *J. Allergy Clin. Immunol.* **96**,901–905.
135. Heymann, W.R. (1999), *J. Am. Acad. Dermatol.* **40**,229–232.
136. Koh, C.K., Hew, F.L., and Chiu, C.L. (2000), *Ann. Acad. Med. Singapore* **29**,528–531.
137. Shiotani, A., Okada K., Yanaoka, K., et al. (2001), *Helicobacter* **6**,60–65.
138. Liutu, M., Kalimo, K., and Uksila, J. (1998), *Int. J. Dermatol.* **37**,515–519.
139. Hook-Nikanne, J., Varjonen, E., Harvima, R.J., et al. (2000), *Acta Derm. Venereol.* **80**,425–426.
140. Dauden, E., Jimenez-Alonso, I., and Garcia-Diez, A. (2000), *Int. J. Dermatol.* **39**,446–452.
141. Schnyder, B., Helbing, A., and Pichler, W.J. (1999), *Int. Arch. Allergy Immunol.* **119**,60–63.
142. Greer, K.E. Dapsone and sulfapyridine, in *Systemic Drugs for Skin Diseases*, Wolverson and Wilkins, eds., W.B. Saunders Co., Philadelphia, 1991, pp. 247–264.
143. Warin, R.P. and Champion, R.H. Acute and chronic urticaria: clinical features, in *Urticaria*, Warin, R.P. and Champion, R.H., eds., W.B. Saunders Co., Ltd., 1974, pp. 83–85.
144. Schnyder, B., Helbling, A., and Pichler, W.J. (1999), *Int. Arch. Allergy Immunol.* **119**,60–63.
145. Tharp, M.D. (1996), *J. Allergy Clin. Immunol.* **98**,S325–S330.
146. Harris, A., Twarog, F.J., and Geha, R.S. (1983), *Ann. Allergy* **51**,161–165.
147. Kaplan, A.P. Urticaria and angioedema, in *Allergy: Principles & Practice*, Middleton, Reed, Ellis, et al., eds., Mosby, St. Louis, 1998, p. 1104.
148. Soter, N.A. and Wasserman, S.I. IgE-dependent urticaria and angioedema in *Dermatology in General Medicine*, 3rd ed., Fitzpatrick, Eisen, Wolff, et al., eds., McGraw-Hill Book Co., New York, 1987, pp. 1282–1283.
149. Harber, L.C. and Bickers, D.R. Solar urticaria, in *Photosensitivity Diseases*, 2nd ed., Harber and Bickers, eds., B.C. Decker, Inc., Toronto, 1989, p. 211.