TABLE 376-1 CLASSIFICATION OF URTICARIA AND/OR ANGIOEDEMA

1. **IgE-dependent**
   a. Specific antigen sensitivity (pollens, foods, drugs, fungi, molds, Hymenoptera venom, helminths)
   b. Physical: dermographism, cold, solar, pressure, cholinergic
   c. Autoimmune
2. **Bradykinin-mediated**
   a. Hereditary angioedema: C1 inhibitor deficiency: null (type 1) and dysfunctional (type 2); mutated factor XII (type 3)
   b. Acquired angioedema: C1 inhibitor deficiency: anti-idiotype and anti-C1 inhibitor
   c. Angiotensin-converting enzyme inhibitors
3. **Complement-mediated**
   a. Necrotizing vasculitis
   b. Serum sickness
   c. Reactions to blood products
4. **Nonimmunologic**
   a. Direct mast cell–releasing agents (opiates, antibiotics, curare, D-tubocurarine, radiocontrast media)
   b. Agents that alter arachidonic acid metabolism (aspirin and nonsteroidal anti-inflammatory agents, azo dyes, and benzoates)
5. **Idiopathic**

angioedema elicited by ingestion of fresh fruits, shellfish, fish, milk products, chocolate, legumes including peanuts, and various drugs that may elicit not only the anaphylactic syndrome with prominent gastrointestinal complaints but also urticaria alone.

Additional etiologies include physical stimuli such as cold, heat, solar rays, exercise, and mechanical irritation. The physical urticarias can be distinguished by the precipitating event and other aspects of the clinical presentation. *Dermographism*, which occurs in 1–4% of the population, is defined by the appearance of a linear wheal at the site of a brisk stroke with a firm object or by any configuration appropriate to the eliciting event (Fig. 376-3). Dermographism has a prevalence that peaks in the second to third decades. It is not influenced by atopy and has a duration generally of <5 years. *Pressure urticaria*, which often accompanies chronic idiopathic urticaria, presents in response to a sustained stimulus such as a shoulder strap or belt, running (feet), or manual labor (hands). *Cholinergic urticaria* is distinctive in that the pruritic wheals are of small size (1–2 mm) and are surrounded by a large area of erythema; attacks are precipitated by fever, a hot bath or shower, or exercise and are presumptively attributed to a rise in core body temperature. *Exercise-induced anaphylaxis* can be precipitated by exertion alone or can be dependent on prior food ingestion. There is an association with the presence of IgE specific for α-5 gliadin, a component of wheat. The clinical presentation can be limited to flushing, erythema, and pruritic urticaria but may progress to angioedema of the face, oropharynx, larynx, or intestine or to vascular collapse; it is distinguished from cholinergic urticaria by presenting with wheals of conventional size and by not occurring with fever or a hot bath. *Cold urticaria* is local at body areas exposed to low ambient temperature or cold objects but can progress to vascular collapse with immersion in cold water (swimming). *Solar urticaria* is subdivided into six groups by the response to specific portions of the light spectrum. *Vibratory angioedema* may occur after years of occupational exposure or can be idiopathic; it may be accompanied by cholinergic urticaria. Other rare forms of physical allergy, always defined by stimulus-specific elicitation, include *local heat urticaria*, *aquagenic urticaria* from contact with water of any temperature (sometimes associated with polycythemia vera), and *contact urticaria* from direct interaction with some chemical substance.

Dermographism

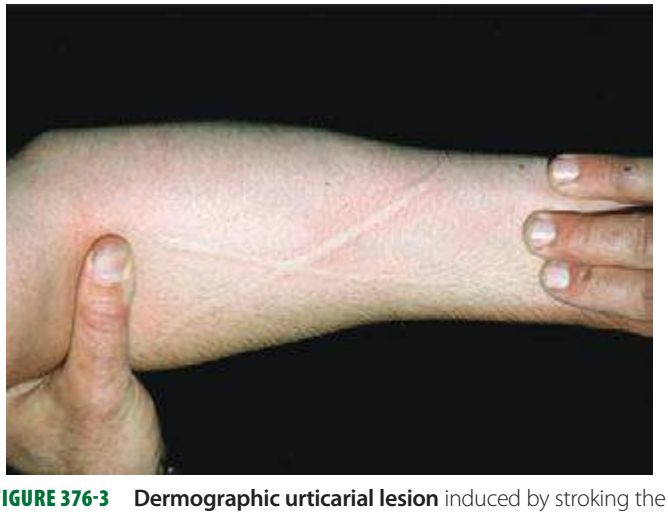

FIGURE 376-3 Dermographic urticarial lesion induced by stroking the forearm lightly with the edge of a tongue blade. The photograph, taken after 2 minutes, demonstrates a prominent wheal-and-flare reaction in the shape of an *X*. *(From LA Goldsmith et al [eds]: Fitzpatrick's Dermatology in General Medicine, 8th ed. New York, McGraw-Hill, 2012. Photograph provided by Allen P. Kaplan, MD, Medical University of South Carolina.)*

Angioedema without urticaria due to the generation of bradykinin occurs with C1 inhibitor (C1INH) deficiency that may be inborn as an autosomal dominant characteristic or may be acquired through the appearance of an autoantibody. The angiotensin-converting enzyme (ACE) inhibitors can provoke a similar clinical presentation in 0.1–0.5% of hypertensive patients due to attenuated degradation of bradykinin. The urticaria and angioedema associated with classic serum sickness or with hypocomplementemic cutaneous necrotizing angiitis are believed to be immune-complex diseases. The drug reactions to mast cell granule–releasing agents and to NSAIDs may be systemic, resembling anaphylaxis, or limited to cutaneous sites.

PATHOPHYSIOLOGY AND MANIFESTATIONS

Urticarial eruptions are distinctly pruritic, may involve any area of the body from the scalp to the soles of the feet, and appear in crops of 12- to 36-h duration, with old lesions fading as new ones appear. Most of the physical urticarias (cold, cholinergic, dermatographism) are an exception, with individual lesions lasting less than 2 h. The most common sites for urticaria are the extremities and face, with angioedema often being periorbital and in the lips. Although self-limited in duration, angioedema of the upper respiratory tract may be life-threatening due to laryngeal obstruction, whereas gastrointestinal involvement may present with abdominal colic, with or without nausea and vomiting, and may result in unnecessary surgical intervention. No residual discoloration occurs with either urticaria or angioedema unless there is an underlying vasculitic process leading to superimposed extravasation of erythrocytes.

The pathology is characterized by edema of the superficial dermis in urticaria and of the subcutaneous tissue and deep dermis in angioedema. Collagen bundles in affected areas are widely separated, and the venules are sometimes dilated. Any perivenular infiltrate consists of lymphocytes, monocytes, eosinophils, and neutrophils that are present in varying combination and numbers.

Perhaps the best-studied example of IgE- and mast cell–mediated urticaria and angioedema is *cold urticaria*. Cryoglobulins or cold agglutinins are present in up to 5% of these patients. Immersion of an extremity in an ice bath precipitates angioedema of the distal portion with urticaria at the air interface within minutes of the challenge. Histologic studies reveal marked mast cell degranulation with associated edema of the dermis and subcutaneous tissues. The histamine level in the plasma of venous effluent of the cold-challenged and angioedematous extremity is markedly increased, but no such increase appears in the plasma of effluent of the contralateral normal extremity. Elevated levels of histamine have been found in the plasma of venous effluent and in the fluid of suction blisters at experimentally induced lesional sites in patients with dermographism, pressure urticaria, vibratory angioedema, light urticaria, and heat urticaria. By ultrastructural analysis, the pattern of mast cell degranulation in cold urticaria resembles an IgE-mediated response with solubilization of granule contents, fusion of the perigranular and cell membranes, and discharge of granule contents, whereas in a dermographic lesion, there is additional superimposed zonal (piecemeal) degranulation. There are several reports of