

## Urticaria

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Urticaria is a problem often as vexing to the physician as to the patient. The approach to the patient with hives first demands a search for the etiology, whether endogenous and triggered by emotions or occult systemic disease, exogenous and triggered by allergy to inhaled or ingested antigens, or physical and due to abnormal sensitivity to heat, cold, light, or pressure. Often a fruitless search, the diagnostic evaluation must be accompanied by appropriate symptomatic therapy requiring familiarity with the antihistamines and their relative advantages in the various forms of urticaria. Elimination diets are of diagnostic as well as therapeutic value: penicillin-free, yeast-free, and salicylate-free diets are particularly useful. Therapeutic trials of tetracycline, nystatin and griseofulvin may be helpful, while corticosteroids and specific desensitization are rarely of value.

Urticaria, or hives, is among the easiest of dermatologic disorders to diagnose, and often one of the most frustrating to treat. The lesions are transient wheals which appear suddenly, itch or burn, and fade rapidly. Some authorities<sup>1</sup> permit a diagnosis of urticaria even if individual lesions persist up to 48 hours, but the diagnosis should be carefully scrutinized in any patient whose lesions persist longer than eight hours.

Urticaria may be acute (a single episode of a few days duration), chronic (over an arbitrarily designated six-week period), or recurrent. Angioedema (giant hives) occurs when hives form in deeper, subcutaneous tissues. The term angioedema is preferred over angioneurotic edema because this entity is no more psychogenic ("neurotic") than any other form of hives.

Evaluation and treatment of urticaria presents a twofold problem: the search for the specific cause and the search for a satisfactory treatment.

### Pathogenesis of Urticaria

The hive is the result of a localized increase in vascular permeability with the resulting exudation of fluid and protein. Most often this change in vascular permeability appears to be mediated by histamine released from mast cells — the phenomenon of mast cell degranulation. Other mediators of wheal formation include bradykinin and other kinins, serotonin, slow-reacting substance (SRS), prostaglandins, and certain complement factors. Acetylcholine intradermally may cause hives in some patients; it certainly plays a significant, if as yet uncharacterized, role in cholinergic urticaria.

The underlying abnormality in urticaria is unclear; an allergic basis cannot be demonstrated in a number of cases. In hereditary angioedema, a specific deficiency of a complement (C1r) inhibitor has been demonstrated, and it seems likely that some cases of chronic urticaria may be attributable

to abnormalities in homeostasis of mediators, activators, and inhibitors.

The immunologic mechanisms of urticaria are probably limited to the reactions classified as types I and III. In type I reactions, antibody, probably IgE, combines with antigen and with the mast cell membrane, resulting in the release of histamine-containing mast cell granules. Complement is not involved. The type III reaction involves soluble antigen-antibody complexes which, in the presence of complement, result in damage to cells and the release of active mediator substances.

### The Diagnostic Work-up of Urticaria

The history is often most useful in determining precipitating factors. Recurrent urticaria may be correlated with the pollen season, the heating season (house dust), exposure to animals, dietary changes, exercise, sunlight, heat, and cold. Chronic urticaria may be temporally related to use of laxatives, analgesics, sedatives, or other medications.

The physical examination may be least useful. A pigmented lesion which urticates when stroked is the cutaneous mastocytoma or urticaria pigmentosa; dermatographism may be diagnosed on physical examination. Rarely, an occult malignancy, infection, or collagen disease may be discovered.

Laboratory studies are listed in Table 1. The extent of laboratory investigation must be determined by the examining physician, taking into consideration the chronicity of the eruption as well as the findings on initial examination.

The most frequently cited causes of hives are food and drug allergies, infections, and according to some authorities, emotional factors. Table 2 illus-

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**Table 1. Approach to Urticaria**

Initial evaluation
History and physical
CBC and differential
Routine chemistries
(as indicated by history and physical)
Urinalysis and culture
LE clot, antinuclear antibody,
rheumatoid factor
VDRL
Thyroid function tests
Cryoglobulins
Salicylate level, salicylate-free diet
Test for dermatographism, cold urticaria
In-depth survey
Basic elimination diet
Penicillin-free diet
Stool ova and parasites
X-rays: dental, sinus, chest,
gallbladder
Profound search
Trials (2 weeks) of:
Nystatin (with yeast-free diet)
Tetracycline
Griseofulvin
X-rays: GI, IVP
Strict elimination diet

**Table 2. Etiological Classification of Urticarias**

Physicochemical urticarias
Dermographism
Cholinergic urticaria
Cold urticaria
Solar urticaria
Heat urticaria
Aquagenic urticaria
Endogenous causes
Infections and infestations
Bacteria — sinusitis, dental infections
Viruses — hepatitis, mononucleosis
Fungi + yeasts — tinea, candidosis
Amebae
Helminths
Collagen diseases — SLE
Neoplasms
Psychogenic causes
Exogenous causes
Inhalants
Food
Drugs
Miscellaneous
Hereditary angioedema
Urticaria pigmentosa

**Table 3. Salicylate-Free Diet\* (Modified from Feingold)<sup>3</sup>**

Omit: Almonds
Apples
(cider and cider vinegars)
Apricots
Berries (all)
Cherries
Cloves
Cucumbers (and pickles)
Currants
Grapes and raisins
Lemons
Mint flavors
Melons
Nectarines
Oranges
Peaches
Peppers (and tabasco)
Plums and prunes
Tea
Tomatoes
Oil of wintergreen

\*A stricter and more complex form of this diet which also omits cross reacting food additives is given by Noid et al.<sup>2</sup>

attack in this way the afternoon before the prom — and will remain clear for hours after.

### Cold Urticaria (Table 4)

Familial cold urticaria is a rare condition in which generalized exposure to cold can cause burning erythema, wheals, fever, leukocytosis, and occasionally collapse. Acquired cold urticaria is most often precipitated by contact with cold water or cold objects (such as a glass containing ice cubes). An ice cube may be held to the skin for up to ten minutes as a test; hives will appear either immediately or shortly after rewarming. Diseases listed in the table must be ruled out. Treatment is unsatisfactory, but large doses of penicillin have been successful in some cases.<sup>4</sup> Cyproheptadine hydrochloride (Periactin) may be superior to the other antihistamines.

### Solar Urticaria

Some individuals develop hives on exposed areas after exposure to sunlight for 30 seconds or more. The eruption is usually wavelength specific, and with the development of similarly specific sunscreens, such as Presun or Uval, many of these patients may go outdoors without symptoms. Antihistamines are helpful but require high dosages. These patients are best referred for specialized phototesting if sunscreens fail to provide adequate control.

### Heat Urticaria and Aquagenic Urticaria

Induced by contact with hot objects and water respectively, these are medical curiosities. Treatment is limited to avoidance of the exciting stimulus whenever possible, since antihistamines are of little value. There is no apparent relationship to underlying disease.<sup>5,6</sup>

### Endogenous Causes of Urticaria

A variety of infections have been reported as causing chronic urticaria; a number of these are listed in Table 2. Urticaria has been reported as a prodrome in up to one third of patients with hepatitis; hives are also not uncommon in mononucleosis and after smallpox vaccination. Occult bacterial infection is often associated with hives, and special attention must be directed toward the possible focus of infection in the teeth, sinuses, gall-

exaggerated flare and wheals along the course of the scratch. The wheals are pruritic; they may be elicited by scratching or rubbing, by the pressure of constricting garments, or by other forms of blunt trauma to the skin. Salicylates are often implicated as potentiating the episodes of dermatographism, and the blood level of salicylate should be measured. If salicylate is present, a salicylate-free diet (Table 3) may be prescribed.<sup>2</sup> Dermatographism will often respond to antihistamines, but hydroxyzine is usually most effective.

### Cholinergic Urticaria

This form of urticaria may often be diagnosed by characteristic, small, 2 to 3 mm evanescent wheals which are evoked by those stimuli which induce sweating: exercise, generalized heat (a sauna), or emotional tension. The diagnosis may be confirmed by having the patient exercise to the point of profuse sweating; the characteristic hives should appear. Intradermal Mecholyl (0.02 percent) or nicotine (1:100,000) could be given to elicit the localized reaction — a large wheal and a flare, studded with small wheals. Antihistamines are of limited value, but they may be used concurrently with hot baths or exercise sufficient to provoke an attack which would then be followed by a refractory period. A teenager, for example, may provoke an

trates an etiological classification of urticaria which may be found useful.

### The Physicochemical Urticarias

#### Dermographism

Also called factitious urticaria, dermatographism is an exaggeration of the triple response of Lewis. Skin which is firmly scratched with a fingernail or tongue blade develops an

**Table 4. Causes of Cold Urticaria**

- Essential Cold Urticaria
- Hereditary
- Acquired
- Cryoglobulinemia
- Monoclonal
- Myeloma
- Macroglobulinemia
- Mixed
- Systematic Lupus
- Paroxysmal Cold Hemoglobinuria (Syphilis)

bladder, female pelvic organs, prostate, or urinary tract.

Fungi may also instigate hives. Candidosis (moniliasis) and dermatophytosis (tinea) must be ruled out, and if present should be treated vigorously. Skin tests to *Candida* may be very useful, and when positive, oral (and vaginal) nystatin combined with a yeast-free diet (Table 5) has been quite successful.<sup>7</sup> Bacterial or other fungal (dermatophyte) skin tests have not given similarly useful results.

Parasitic infestations commonly cause hives; stools should be examined routinely for ova and parasites and a significant elevation in eosinophil count may alert the clinician to the presence of parasites even with a negative stool examination.

Collagen diseases may be first manifested as hives.<sup>8</sup> As many as seven percent of systemic lupus erythematosus patients may have urticaria, and rheumatoid arthritis may also present with hives or hive-like lesions. Similarly, the onset of hyperthyroidism may be signalled by hives.<sup>9</sup>

Psychological factors appear to play a significant role in a number of patients with urticaria. Up to 25 percent of patients in various series have been found to have significant psychological factors; often the patient himself will point out the role of emotional stress. On the other hand, it is most important that the physician not fall into the error of blaming all urticaria on "nerves."

**Exogenous Causes of Urticaria**

*Inhalant allergy* may be the cause of hives as well as asthma or hay fever. Hives may be triggered by aerosols (inhaled hair spray or insecticide), animal danders, pollen, dust, or mold. The history is useful here, since the value of skin testing using the prick or

Table 5. Penicillin-Free Diet	
Omit:	Milk Cottage cheese Chocolate Root beer Vinegar
	Cheese Commercial bakery products Fermented beverages Pickles
Yeast-Free Diet	
Omit:	Cheese (all kinds) Buttermilk Mayonnaise Olives Pickles Sauerkraut Horseradish Tomato Sauce Catsup Chili peppers
	Bread and baked goods Gerber's oatmeal and barley cereal All fermented beverages Root beer and ginger ale Malt products (cereals, malted candy) All vinegar (including salad dressings) Vitamins Milk fortified with vitamins Processed meats (frankfurters, luncheon meats) Mince pie

scratch test is controversial. Most authorities seem to feel that it does *not* represent a useful approach to diagnosis.

*Food allergies*, though often obvious, may be very difficult to track down. The first step is to have the patient keep a food diary for two weeks correlating severity of hives with foods eaten. If this method fails to reveal a causative food, the basic elimination diet (elimination diet #1, Table 6) may be followed for two weeks. If the patient still has hives, a very strict elimination diet may then be prescribed for one week (elimination diet #2, Table 6).

It is important to recognize that a number of food additives used in commercial food processing may be common to a variety of packaged foods; all elimination diet meals must be prepared at home.

*Drug ingestion* is a frequent cause of hives. It is unnecessary to test the common offenders — any drug, whether taken by mouth or inserted in any other bodily orifice, may be responsible for hives. Aspirin and tartrazine, a related yellow dye commonly used as a food coloring, are frequent offenders.<sup>2</sup> The mechanism of their action may involve potentiation of urticaria or dermatographism originally elicited by other substances, and salicylate avoidance may result in improvement without complete clearing.

Penicillin allergy may result in hives following consumption of dairy products containing minimal amounts of penicillin, obtained from cattle treated with the antibiotic. Although the milk so derived is not supposed to be sold, occasional unscrupulous farmers fail to

Table 6. Elimination Diet 1	
Omit the following foods:	
Eggs	Tomatoes
Chocolate	Pork
Bananas	Milk
Nuts	Cheese
Coffee	Citrus Fruits
Fish, seafood	Alcoholic beverages
Berries	Grapes
Corn	Pineapple
Cottonseed oil	Liver
Elimination Diet 2	
Omit all foods except:	
Rice, rice wafers	
Rye-Krisp	
Lamb (broiled, salt only seasoning)	
Tea	
Prunes	
Add raw vegetables rarely or never eaten after 72 hours.	

remove cows under treatment from their herds. The penicillin, filtered through the cows' udders, is still a potent allergen. A penicillin free diet (Table 5) is useful for the rare patient with exquisite penicillin sensitivity, and should be routinely tried in any case of urticaria on a patient with known penicillin sensitivity.

**Treatment of Urticaria**

The most important step in the treatment of urticaria is the identification and elimination of the inciting stimulus, following the approach outlined in Table 1, and if necessary, utilizing the diets in Tables 3 to 6. Antihistamines are the mainstay of drug treatment, but must be recognized as purely symptomatic therapy. Diphenhydramine hydrochloride

(Benadryl) and chlorpheniramine maleate (Chlor-Trimeton) are the most commonly used effective antihistamines. Cyproheptadine hydrochloride (Periactin) has the advantage of additional anti-serotonin activity, and there is some evidence that it is a superior antihistamine in cold urticaria. Hydroxyzine (Atarax, Vistaril) is particularly useful in dermatographism and the physical (solar, cholinergic) urticarias. Its tranquilizing effect may account, in part, for its superiority in urticaria of unknown etiology. The dosage must be pushed to tolerance and mild sedation is not altogether undesirable.

Antihistamine therapy should be constant, rather than intermittent, and once the hives are suppressed, the dosage should be slowly reduced after a period of weeks.

In recalcitrant urticaria of unknown cause, it is not unreasonable to prescribe therapeutic trials of tetracycline, griseofulvin, and nystatin (orally and vaginally), each drug being given alone for a two-week period.

Epinephrine, 1:1,000 0.5 cc subcutaneously or intramuscularly, is useful in aborting an attack of hives. Ephedrine sulfate, 15 to 30 mg, may also be taken (early in the day) to maintain suppression of urticaria. Sympathomimetic drugs such as these

are particularly useful in angioedema, and should be accompanied by potent doses of antihistamines.

Corticosteroids in the routine treatment of urticaria are only of occasional value and prolonged use of steroids generally must be condemned. The dosage required for complete suppression of wheals is often high, and adverse side effects are common. Occasionally, steroids are beneficial in aborting acute, severe episodes of urticaria when used in conjunction with epinephrine and antihistamines.

Calcium gluconate is an old-fashioned remedy for hives. It is unclear whether calcium is anything more than a placebo; the rationale for its use is unclear. In difficult cases, 1 to 5 gm of calcium gluconate by mouth or 10 cc of 10 percent calcium gluconate intramuscularly is occasionally helpful.

Specific desensitization to inhalent antigens is theoretically a rational approach. In practice, however, results are inferior to the results in hay fever and asthma.

Autohemotherapy, an irrational form of therapy in which 10 to 20 cc of blood, freshly drawn from the vein, is immediately injected into the buttock, was once a common treatment. In stubborn cases, "persistent urticaria with a desperate patient and physi-

cian,"<sup>1</sup> such injections may be given once weekly.

Heparin, vitamin K, nicotinic acid, procaine, and pronestyl have been evaluated and found wanting.

In summary, the patient with hives deserves an extensive investigation in order to demonstrate the etiology of his eruption, and treatment should be directed at the underlying cause whenever possible. If an underlying cause can neither be found nor corrected, antihistaminic drugs are most useful, if given continuously, in sufficient dosage, and withdrawn slowly.

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